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Ambient Water Quality Criteria for Zinc

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16. ABSTRACT

Section 304(A) of the Clean Water Act [33 U.S.C. 1314(A)], requires EPA to publish and periodically update water quality criteria. These criteria are to reflect the latest scientific knowledge on the identifiable effects of pollutants on public health and welfare, aquatic life, and recreation. This report presents water quality criteria for Zinc. It presents concentration criteria for the protection of freshwater and saltwater aquatic life. It presents 'safe' concentrations for humans, and in the case of suspect or proven carcinogens, gives various levels of incremental cancer risk. A Section 304(A) water quality criterion is a qualitative or quantitative estimate of the concentration of a water constituent or pollutant in ambient waters which, when not exceeded, will ensure a water quality sufficient to protect a specified water use. Under the Act a criterion is a scientific entity, based solely on data and scientific judgment. It does not reflect considerations of economic or technological feasibility nor is it a water quality standard and in itself has no regulatory effect.

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ZINC

Prepared By
U.S. ENVIRONMENTAL PROTECTION AGENCY

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FOREWORD

Section 304 (a)(1) of the Clean Water Act of 1977 (P.L. 95-217), requires the Administrator of the Environmental Protection Agency to publish criteria for water quality accurately reflecting the latest scientific knowledge on the kind and extent of all identifiable effects on health and welfare which may be expected from the presence of pollutants in any body of water, including ground water. Proposed water quality criteria for the 65 toxic pollutants listed under section 307 (a)(1) of the Clean Water Act were developed and a notice of their availability was published for public comment on March 15, 1979 (44 FR 15926), July 25, 1979 (44 FR 43660), and October 1, 1979 (44 FR 56628). This document is a revision of those proposed criteria based upon a consideration of comments received from other Federal Agencies, State agencies, special interest groups, and individual scientists. The criteria contained in this document replace any previously published EPA criteria for the 65 pollutants. This criterion document is also published in satisifaction of paragraph 11 of the Settlement Agreement in Natural Resources Defense Council, et. al. vs. Train, 8 ERC 2120 (D.D.C. 1976), modified, 12 ERC 1833 (D.D.C. 1979).

The term "water quality criteria" is used in two sections of the Clean Water Act, section 304 (a)(1) and section 303 (c)(2). The term has a different program impact in each section. In section 304, the term represents a non-regulatory, scientific assessment of ecological effects. The criteria presented in this publication are such scientific assessments. Such water quality criteria associated with specific stream uses when adopted as State water quality standards under section 303 become enforceable maximum acceptable levels of a pollutant in ambient waters. The water quality criteria adopted in the State water quality standards could have the same numerical limits as the criteria developed under section 304. However, in many situations States may want to adjust water quality criteria developed under section 304 to reflect local environmental conditions and human exposure patterns before incorporation into water quality standards. It is not until their adoption as part of the State water quality standards that the criteria become regulatory.

Guidelines to assist the States in the modification of criteria presented in this document, in the development of water quality standards, and in other water-related programs of this Agency, are being developed by EPA.

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Aquatic Life Toxicology

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CRITERIA DOCUMENT

ZINC

CRITERIA

Aquatic Life

For total recoverable zinc the criterion to protect freshwater aquatic life as derived using the Guidelines is 47 µg/l as a 24-hour average and the concentration (in µg/l) should not exceed the numerical value given by $e^{(0.83[\ln(\text{hardness})]+1.95)}$ at any time. For example, at hardnesses of 50, 100, and 200 mg/l as $CaCO_3$ the concentration of total recoverable zinc should not exceed 180, 320, and 570 µg/l at any time.

For total recoverable zinc the criterion to protect saltwater aquatic life as derived using the Guidelines is 58 µg/l as a 24-hour average and the concentration should not exceed 170 µg/l at any time.

Human Health

Sufficient data are not available for zinc to derive a level which would protect against the potential toxicity of this compound. Using available organoleptic data, for controlling undesirable taste and odor quality of ambient water, the estimated level is 5 mg/l. It should be recognized that organoleptic data as a basis for establishing a water quality criteria have limitations and have no demonstrated relationship to potential adverse human health effects.

INTRODUCTION

Zinc is a bluish-white metal which dissolves readily in strong acids. Its principal uses include electroplating and the production of alloys. Zinc is never found free in nature, but occurs as the sulfide, oxide, or carbonate (Lange, 1956).

Zinc has an atomic number of 30 and its atomic weight is 65.38 (Weast, 1977). The chemistry of zinc is similar to that of cadmium, which is directly below it in the periodic table (Cotton and Wilkinson, 1972). In aqueous solution, zinc always has a valence of +2, and it exhibits amphoteric propertiers, dissolving in acids to form hydrated Zn(II) cations and in strong bases to form zincate anions [probably $Zn(OH)_4^{-2}$]. Compounds of zinc with the common ligands of surface waters are soluble in neutral and acidic solutions, so that zinc is readily transported in most natural waters and is one of the most mobile of the heavy metals. The geochemistry of zinc in surface water has been extensively reviewed by Hem (1972). Since the divalent zinc ion does substitute to some extent for magnesium in the silicate minerals of igneous rocks, weathering of this zinc-containing bedrock gives rise to Zn^{+2} in solution whereupon the hydrated cation remains dominant to pH values of about 9. Zinc forms complexes with a variety of organic and inorganic ligands, but these compounds are sufficiently soluble to prevent their becoming a limiting factor for the solubility of the small concentrations of zinc found in most aquatic environments. Adsorption on clay minerals, hydrous oxides, and organic matter is a more probable limiting mechanism.

Most of the zinc introduced into the aquatic environment is partitioned into the sediments by sorption onto hydrous iron and manganese oxides, clay minerals, and organic materials. Precipitation of the sulfide is an important control on the mobility of zinc in reducing environments, and precipitation of the hydroxide, carbonate, or basic sulfate can occur where zinc is present in high concentrations. Formation of complexes with organic and inorganic ligands can increase the solubility of zinc and probably increases the tendency for zinc to be adsorbed.

Sorption of zinc by hydrous metal oxides, clay minerals, and organic materials is probably the dominant fate of zinc in the aquatic environment. The tendency of zinc to be sorbed is affected not only by the nature and concentration of the sorbent but by pH and salinity as well. In a study of heavy metal adsorption by two oxides and two soils, zinc was completely removed from solution when pH exceeded 7; below pH 6, little or no zinc was adsorbed. Addition of inorganic complexing ligands enhanced the affinity for adsorption (Huang, et al. 1977).

Helz, et al. (1975) found that zinc is desorbed from sediments as salinity increases. This phenomenon, which is exhibited by many of the other metals as well, is apparently due to displacement of the adsorbed zinc ions by alkali and alkaline earth cations which are abundant in brackish and saline waters. In summary, sorption is the dominant fate process affecting zinc, and it results in enrichment of suspended and bed sediments relative to the water column. Variables affecting the mobility of zinc include the concentration and composition of suspended and bed sediments, dissolved and particulate iron and manganese concentrations, pH, salinity, concentration of complexing ligands, and the concentration of zinc.

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Aquatic Life Toxicology*

INTRODUCTION

Acute toxicity tests have been conducted with thirty species of freshwater animals, and the median toxicity values range from 90 to 58,100 µg/l. Chronic tests with six species have resulted in chronic values from 47 to 852 µg/l. With nine different plant species the results ranged from 30 to 67,700 µg/l.

The zinc data base for saltwater organisms includes the results of acute toxicity tests with twenty-one species of invertebrates and three species of fishes. Zinc was acutely toxic to the mummichog at 83,000 µg/l and at 166 µg/l to the hard-shelled clam. A chronic value of 166 µg/l is available from a life-cycle test with a mysid shrimp, and residue data are reported for five species of algae and nine species of invertebrates. Decreased growth of various plants was reported at concentrations ranging from 50 to 25,000 µg/l.

Zinc is a common trace constituent of natural waters and is a required trace element in the metabolism of most organisms. The uptake of zinc from the environment, either via ingestion or absorption, must exceed some minimum rate in order for an organism to function properly. Whether any waters are deficient in zinc content from the standpoint of the existing biota is not clear, but the question is probably moot with regard to water quality criteria for zinc.

Above some theoretical minimum concentration of zinc in water, there exists a range of zinc concentrations which is readily tolerated through each organism's capacity to regulate the uptake, internal distribution, and excretion of zinc. This range undoubtedly varies among individuals, species, and larger phylogenetic groups. In addition, this ability, and hence the tolerated range, probably varies with the range of zinc concentrations to which the various populations have been historically exposed and acclimated. Thus, biological variability in zinc tolerance should be expected to occur based on phylogenetic differences and historic exposure patterns, both short-term and geologic in scale.

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*The reader is referred to the Guidelines for Deriving Water Quality Criteria for the Protection of Aquatic Life and Its Uses in order to better understand the following discussion and recommendation. The following tables contain the appropriate data that were found in the literature, and at the bottom of each table are calculations for deriving various measures of toxicity as described in the Guidelines.

Compounding the problem of defining biologically safe zinc concentrations is the occurrence of many different forms of zinc in surface waters. Zinc can occur in both suspended and dissolved forms. Dissolved zinc may occur as the free (hydrated) zinc ion or as dissolved complexes and compounds with varying degrees of stability and toxicity. Some forms of suspended (undissolved) zinc may be readily dissolved following minor changes in water chemistry. Other suspended zinc may be reversibly sorbed onto suspended solids or, conversely, almost irreversibly included in suspended mineral particles.

Paramount to the question of zinc toxicity are the physical and chemical state of the zinc, the toxicity of each form of the zinc, and the degree of interconversion to be expected among the various forms. All zinc forms are presumably nontoxic unless they can be sorbed or bound by biological materials. Conversely, all zinc forms are potentially toxic if they can be sorbed or bound by biological tissues. Most likely, zinc will not be sorbed or bound unless it is dissolved, but some solution of the zinc may reasonably be expected to occur in the alimentary canal following ingestion of particulates containing undissolved zinc. Thus, the toxicity of undissolved zinc to any organism probably depends on feeding habits, with the result that plants and most fish would presumably be relatively unaffected by suspended zinc, but many invertebrates could be adversely affected by ingestion of sufficient quantities of particulates containing zinc.

A complex array of data concerning an assortment of toxic responses to zinc is one result of the physical, chemical, and biological variability described. However, by evaluating the toxicity on a species-by-species basis and by considering several water chemistry parameters, the information can be simplified.

The toxicity of zinc, as well as other heavy metals, is reported to be influenced by a number of chemical factors including calcium, magnesium, hardness, pH, and ionic strength. These factors appear to affect the toxicity of zinc either by influencing the proportion of available zinc or by inhibiting the sorption or binding of available zinc by biological tissues. In freshwater, zinc appears to be less toxic at high hardness levels for a variety of reasons, such as:

1) The ions contributing to hardness, primarily calcium and magnesium, are divalent and compete with zinc, which is also divalent for sites of uptake and binding in biological tissues;

2) Harder waters have higher ionic strengths due to the greater quantity of charged ions (primarily mono- and divalent cations and anions) in solution, and these ions electrostatically inhibit the ability of other ions (including zinc) to approach the absorption or binding sites of the organisms. Basically, zinc ions have lower activity in harder waters; and

3) Generally, harder waters have higher alkalinities and higher pH values. Insoluble, and possibly soluble, zinc carbonate and hydroxide compounds can form which are not sorbed by many organisms. Changes in

hardness, pH, and alkalinity will cause corresponding changes in the toxicity of the zinc in the water.

Hardness, on the other hand, may have scant relationship to the amount of zinc sorbed to or included in particulate material or bound to organic chemicals. Nevertheless, hardness appears to be the single best chemical parameter to reflect the variation in zinc toxicity induced by differences in general water chemistry.

However, water quality criteria for freshwater developed with hardness as the sole physical-chemical variable may be lower than ambient total zinc levels in some surface waters of the United States. This may result, in part, from the current inability to correlate quantitatively the effects on zinc toxicity of physical-chemical factors other than hardness and those factors such as ionic strength, pH, and alkalinity which are qualitatively related to hardness. Alternatively, where zinc levels exceed criteria, the zinc may be harming the biota, or the biota may have evolved as a zinc-resistant population. The actual situation must be evaluated based on the biological, chemical, and physical factors just discussed.

Of the analytical measurements currently available, a water quality criterion for zinc is probably best stated in terms of total recoverable zinc, because of the variety of forms of zinc that can exist in bodies of water and the various chemical and toxicological properties of these forms. The forms of zinc that are commonly found in bodies of water and are not measured by the total recoverable procedure, such as the zinc that is a part of minerals, clays, and sand, probably are forms that are less toxic to aquatic life and probably will not be converted to the more toxic forms very readily under natural conditions. On the other hand, forms of zinc that are commonly found in bodies of water and are measured by the total recoverable procedure, such as the free ion, and the hydroxide, carbonate, and sulfate salts, probably are forms that are more toxic to aquatic life or can be converted to the more toxic forms under natural conditions.

Because the criteria are derived on the basis of tests conducted on soluble inorganic salts of zinc, the total zinc and total recoverable zinc concentrations in the tests would probably be about the same and a variety of analytical procedures would produce about the same results. Except as noted, all concentrations reported herein are expected to be essentially equivalent to total recoverable zinc concentrations. All concentrations are expressed as zinc, not as the compound.

EFFECTS

Acute Toxicity

Zinc produces acute toxicity to freshwater organisms over a range of concentrations from 90 to 58,100 μg/l (Table 1). The range of acute median effect concentrations is similar for freshwater fish and invertebrates, with ranges of 90 to 40,900 and 100 to 58,100 μg/l, respectively. A portion of this range is due to hardness related factors, and the remainder is due to species differences and other biological and physical-chemical factors.

Within the larger data sets for individual fish species, especially those for rainbow trout and fathead minnow, the lower LC_{50} values at a given hardness were obtained using younger, smaller fish. Also, acute toxicity tests conducted by Cairns, et al. (1978) with both *Daphnia magna* and *Daphnia pulex* at 5, 10, 15, 20 and 25°C (Tables 1 and 6) showed that acute toxicity increased as temperature increased. The value at 20°C in Table 1 was used in the calculation of the species mean acute intercept because acute and chronic tests with daphnids are usually conducted at this temperature.

An exponential equation was used to describe the observed relationship of the acute toxicity of zinc to hardness in freshwater. Least squares regression of the natural logarithms of the acute values on the natural logarithms of hardness was used to calculate slopes for 10 species (Table 1). Five of the slopes were significant, two were not significant, and the other three could not be tested because only two values were available. The arithmetic mean (0.83) of the five significant slopes was used with the geometric mean toxicity value and hardness for each species to obtain a logarithmic intercept for each of the 29 freshwater species for which acute values are available for zinc. The species mean acute intercept, calculated as the exponential of the logarithmic intercept, was used to compare the relative acute sensitivities (Table 3).

Interestingly, all tests with 10 of the 12 species reported to be more resistant than bluegill (Table 3) were tested in several series of experiments reported by Rehwoldt, et al. (1971, 1972, 1973) conducted in Hudson River water. Whether the water reduced the toxicity of the zinc or whether the species tested were really more resistant cannot be determined. Many of the invertebrates tested by Rehwoldt and his co-workers are known to be generally resistant to heavy metals, so species resistance is a likely explanation. One species tested by Rehwoldt, et al. (1971, 1972), the striped bass, was rather sensitive to zinc, but other investigators obtained acute values which were quite a bit lower for this species.

A freshwater Final Species Acute Intercept of 7.02 µg/l was obtained for zinc using the species mean acute intercepts listed in Table 3 and the calculation procedures described in the Guidelines. Thus the Final Acute Equation is $e^{(0.83[\ln(\text{hardness})] + 1.95)}$.

Acute toxicity data for zinc are available for 21 species of saltwater invertebrates (Table 1) and represent more than two orders of magnitude difference in sensitivity. Larval molluscs were the most sensitive invertebrates with acute values for an oyster of 310 µg/l and for the hard shelled clam of 166 µg/l. Acute values for adult molluscs ranged from 2,500 for the blue mussel to 7,700 for the soft-shelled clam. Zinc was acutely toxic to saltwater polychaetes over the range from 900 µg/l for Neanthes arenaceodentata to 55,000 for Nereis diversicolor. The decapod crustaceans had 96-hour LC_{50} values of 175 and 1,000 µg/l for the lobster and crab, respectively. The reported acute values for copepods ranged from 290 µg/l for Acartia tonsa to 4,090 µg/l for Eurytemora affinis. Results from tests with two mysid shrimp showed similar values; 498 µg/l for Mysidopsis bahia and 591 µg/l for Mysidopsis bigelowi.

The data base for saltwater fishes contains nine values for three species of fish and three taxonomic families (Table 1). The acute values range from 2,730 for larval Atlantic silversides to 83,000 for larval mummichog. Saltwater fish were generally more resistant to acute zinc poisoning than saltwater invertebrates, although there were cases of individual overlap.

The saltwater Final Acute Value for zinc, derived from the Species Mean Acute Values listed in Table 3 using the calculations procedures described in the Guidelines, is 173 µg/l.

Chronic Toxicity

Chronic toxicity tests have been conducted with six species of freshwater organisms (Table 2). Chronic values for five species of fish ranged from 47 µg/l for flagfish (Jordanella floridae) to 852 µg/l for brook trout (Salvelinus fontinalis). No tests of the chronic toxicity of zinc to fish have been conducted in hard water. Four chronic toxicity tests are reported for Daphnia magna, with chronic values ranging from 47 to 136 µg/l. Surprisingly, the chronic toxicity of zinc to this daphnid appears to increase with increasing hardness, a phenomenon which may be attributable to ingestion of precipitated zinc by *Daphnia magna* in hard water tests.

The 10-month chronic toxicity test conducted by Brungs (1969) provided evidence that the chronic value for the fathead minnow in hard water would be below 180 µg/l (Table 6). In light of the 106 µg/l chronic value obtained by Benoit and Holcombe (1978) in soft water, this strongly suggests that the chronic toxicity of zinc to fish may also be relatively unaffected by hardness. Thus, the available toxicity data indicate that hardness effects are much less dramatic for the chronic toxicity of zinc than for acute toxicity, and that the slope of the hardness-toxicity regression may be near zero or even negative for some species.

The only chronic data reported (Table 2) for a saltwater species exposed to zinc are those for the mysid shrimp, *Mysidopsis bahia* (U.S. EPA, 1980). In this flow-through life cycle test the number of spawns recorded at 231 µg/l was significantly ($p<0.05$) fewer than at 120 µg/l, but the number of spawns at 59 and 120 µg/l were not statistically significantly different from those in the control. Brood size was significantly ($p<0.05$) reduced at 231 µg/l but not at lower concentrations. Based upon reproductive data, the lower and upper chronic endpoints were 120 amd 231 µg/l, respectively, which results in a chronic value of 166 µg/l (Table 3).

The acute-chronic ratios derived from the nine chronic tests with zinc in freshwater show a rather wide range (Table 2). Some of the range is due to the differing acute values for different life stages of the same species. Additional variation is due to differences in water quality, but in soft water the values range from less than 1 to 32. It appears that 3 would be a reasonable estimate of an acute-chronic ratio for zinc in freshwater, and this agrees with the only value available in saltwater.

An acute-chronic ratio of 3 used with the freshwater Final Acute Equation (Table 3) would result in a freshwater Final Chronic Equation of $e^{(0.83[\ln(\text{harness})] + 0.85)}$. However, this would result in a Final Chronic Value of 55 µg/l at a hardness of 45 and in higher values at higher hardnesses. Because 47 µg/l is the chronic value for both a sensitive invertebrate in hard water and a medium sensitive fish in soft water, it would appear reasonable to set the freshwater Final Chronic Value at 47 µg/l for all hardnesses. This is also supported by the data suggesting that increasing hardness does not decrease the chronic toxicity of zinc like it decreases the acute toxicity of zinc.

The saltwater Final Acute Value of 173 µg/l divided by an acute-chronic ratio of 3 results in a saltwater Final Chronic Value of 57.7 µg/l (Table 3).

Plant Effects

Results of zinc toxicity tests with nine species of freshwater plants are listed in Table 4. Zinc concentrations from 30 to 21,600 µg/l have been shown to reduce the growth of various plant species. Algae appear to be more sensitive to zinc than macrophytes, with *Selenastrum capricornutum* the most sensitive of the tested algal species. *Selenastrum* sensitivity to zinc is greater in softer waters (Greene, et al. 1975), but the range of hardness values tested was limited (4 to 15 mg/l as $CaCO_3$). The significance of short-term growth inhibition in algae has not been established; however, the existence of growth inhibition at low zinc levels should be considered of potential ecological importance.

Data for the toxic effects of zinc to 13 species of saltwater plants are also listed in Table 4. The growth of kelp was inhibited at 100 µg/l for *Laminaria digitata* (Bryan, 1969) and 250 µg/l for *Laminaria hyperiborea*

(Hopkins and Kain, 1971). The giant kelp, Macrocystis pyrifera, was relatively insensitive to the effects of zinc on photosynthesis with an EC_{50} of 10,000 µg/l.

Microalgae had a wide range of sensitivities to zinc. Growth inhibition was reported at 25,000 µg/l for the diatom, Phaeodactylum tricornutum (Jensen, et al. 1974), for Skeletonema costatum and Thalassiosira pseudonana at 200 µg/l (Braek, et al. 1976), at 100 µg/l for Gymnodinium splendens and Thalassiosira rotula (Kayser, 1977), and at 50 µg/l for Schroederella schroederi (Kayser, 1977).

No freshwater or saltwater Final Plant Value is possible because zinc concentrations were not measured in any of the toxicity tests with plants.

Residues

Table 5 contains bioconcentration factors for zinc determined with two freshwater fish species and two freshwater invertebrate species. The factors for fish were 51 and 432, and those for invertebrate species were 107 and 1,130.

Bioconcentration factors also have been determined for three species of macroalgae and six species of saltwater invertebrates (Table 5), but no data are available for saltwater fishes. The accumulation of zinc by macroalgae varied from a high of 16,600 times ambient for Fucus serratus (Young, 1975) to 1,530 times above ambient for Enteromorpha prolifera (Munda, 1979). Among invertebrate species bioconcentration factors ranged from 20 for the polychaete Nereis diversicolor (Bryan and Hummerstone, 1973) to 16,700 for the oyster Crassostrea virginica (Shuster and Pringle, 1969).

Bioconcentration factors varied considerably among the different species of bivalve molluscs; 43 was obtained with the soft-shell clam (Eisler, 1976b), 500 with the mussel (Pentreath, 1973) and 16,700 with the oyster (Shuster and Pringle, 1969). Bryan (1966) reported zinc accumulation in crab muscle resulting in a bioconcentration factor of 8,800. Because of the variation between species and phyla it is difficult to identify specific trends between bioconcentration and phylogenetic position. Bioconcentration factors for invertebrate species are generally 500 or less except for the crab and oyster.

A Final Residue Value cannot be calculated for either fresh or saltwater because no maximum permissible tissue concentration is available.

Miscellaneous

Table 6 contains other data concerning the effects of zinc on freshwater organisms. Sprague (1968) found that rainbow trout would avoid a zinc concentration of 5.6 µg/l in a laboratory behavior test in water with a hardness of 14 mg/l as $CaCO_3$, but the ecological significance of laboratory avoidance behavior is not known. Sprague (1964b) and Sprague, et al. (1965) emphasized that laboratory avoidance thresholds are probably low estimates, because territorial or migrational motivations would be expected to cause higher thresholds for avoidance in nature. In addition, acclimation to zinc could substantially alter avoidance behavior.

Significant avoidance behavior probably will not occur in nature at zinc concentrations below those required for acute and chronic protection for the most sensitive freshwater organisms. Acclimation and territorial and migratory urges would probably counteract mild aversion to waters containing low zinc concentrations. However, the possibility that a sensitive, nonacclimated species would at least temporarily avoid a body of water with an apparently acceptable zinc concentration cannot be ruled out on the basis of existing data.

Anderson, et al. (1980) reported an average LC_{50} value of 37 µg/l (range 26 to 54 µg/l) for the chironomid *Tanytarsus dissimilis* following 10-day exposure of the embryonic, hatching, and molting stages. Growth of surviving larvae was not significantly affected. Because of the duration and nature of the test and the short life-span of the chironomid tested, this test should probably be considered equivalent to the early life stage test with fish. The sensitivity of this species is further support for a freshwater Final Chronic Value of 47 µg/l.

The data for saltwater aquatic life in Tables 1 and 6 indicate that zinc causes increasing cumulative mortality with increasing time of exposure past 96 hours. Eisler and Hennekey (1977) reported a significant increase in zinc mortality to the mummichog, sandworm, soft-shell clam, and mudsnail when exposures were extended from 4 to 7 days. Benijts-Claus and Benijts (1975) reported delayed development of crab larvae after 16 days exposure at 50 µg/l, indicating cumulative mortality to macrocrustaceans.

Data in Table 6 also indicate a relationship between salinity and acute toxicity. Herbert and Wakeford (1964) reported a decrease in the sensitivity of Atlantic salmon (smolt) and yearling rainbow trout to the acute toxicity of zinc at salinities of 3, 7, and 14 g/kg but an increase in sensitivity at 26 g/kg salinity. The relationship therefore was not linear over the range of salinities tested. Jones (1975) reported a linear increase in mortality with decreasing salinities for both the marine isopod, _Idotea baltica_ and the euryhaline isopod, _Jaera albifrons_.

Molluscan larvae as a taxa are generally more sensitive than the invertebrates to zinc toxicity. Brereton, et al. (1973) reported that reduced development and inhibition of substrate attachment occurred at 125 µg/l with the Pacific oyster, and Nelson (1972) reported that abnormal shell development occurred at 70 µg/l.

Summary

Zinc is an essential trace element which can be toxic at higher concentrations. The acute toxicity of zinc to aquatic organisms is affected by hardness, but the chronic toxicity apparently is not. The range of acute values for freshwater organisms is from 90 to 38,100 µg/l and is similar for fish and invertebrates. Results from chronic toxicity tests indicate a range of chronic values from 47 to 852 µg/l. Of the nine reported chronic toxicity tests, five are tests with fish in soft water and four are tests with Daphnia magna at hardnesses from 45 to 211 mg/l as $CaCO_3$. Chronic zinc toxicity is relatively unaffected by hardness, with zinc possibly becoming more toxic in harder waters. Data from two tests with fathead minnows confirm the apparent inability of hardness to reduce the chronic toxicity of zinc. A chronic value of 47 µg/l was obtained with both a sensitive invertebrate (Daphnia magna) in hard water and a medium sensitive fish (flagfish) in soft water. In addition, a 10-day LC_{50} of 37 µg/l was obtained with a midge.

Although most plants appear to be insensitive to zinc, some values with one species were below 47 µg/l, but other values for the same species were much higher. Data on bioconcentration indicates that concentrations of zinc which do not harm sensitive freshwater organisms will not harm consumers of aquatic organisms. The possibility of avoidance of zinc at low concentrations is suggested by laboratory behavior tests with fish, but the quanititative extrapolation of these results to field situation is apparently not justified.

The saltwater acute values for zinc and fishes ranged from 2,730 µg/l for larval Atlantic silversides to 83,000 for larval mummichog. Acute values for the invertebrate species ranged from 166 for clam larvae to 55,000 for adult polychaetes. The one chronic study conducted with the mysid shrimp produced a chronic value of 166 µg/l resulting in an acutechronic ratio of 3.0. Plant studies with macroalgae reported growth inhibition at 100 µg/l for Laminaria digitata. Microalgae had a wide range of sensitivities to zinc with the lowest value being 50 μg/l for Schroederella schroederi. Bioconcentration factors were generally less than 500 for the commercially important species of invertebrates except for the factors of 16,700 and 8,800 for an oyster and crab, respectively. Zinc mortality is cumulative for exposures beyond four days. The effect of salinity on zinc toxicity appears to be non-linear with fishes and linear with invertebrate species.

CRITERIA

For total recoverable zinc the criterion to protect freshwater aquatic life as derived using the Guidelines is 47 μg/l as a 24-hour average, and the concentration (in μg/l) should not exceed the numerical value given by $e^{(0.83[\ln(\text{hardness})]+1.95)}$ at any time. For example, at hardnesses of 50, 100, and 200 mg/l as $CaCO_3$ the concentration of total recoverable zinc should not exceed 180, 320, and 570 μg/l at any time.

For total recoverable zinc the cirterion to protect saltwater aquatic life as derived using the Guidelines is 58 μg/l as a 24-hour average, and the concentration should not exceed 170 μg/l at any time.

Table 1. Acute values for zinc

Species	Method*	Chemical	Hardness (mg/l as $CaCO_3$)	LC50/EC50** (µg/l)	Species Mean Acute Value** (µg/l)	Reference
			FRESHWATER SPECIES			
Worm, *Nais* sp.	S, M	-	50	16,400	-	Rehwoldt, et al. 1973
Snail, *Physa heterostropha*	S,U	Zinc chloride	43	900***	-	Cairns & Scheier, 1958
Snail, *Physa heterostropha*	S, U	Zinc chloride	41	600***	-	Cairns & Scheier, 1958
Snail, *Physa heterostropha*	S, U	Zinc chloride	165	3,300***	-	Cairns & Scheier, 1958
Snail, *Physa heterostropha*	S, U	Zinc chloride	178	4,400***	-	Cairns & Scheier 1958
Cladoceran, *Daphnia magna*	S, M	Zinc chloride	45	100	-	Biesinger & Christensen, 1972
Cladoceran, *Daphnia magna*	S, M	Zinc sulfate	45	280	-	Cairns, et al. 1978
Cladoceran, *Daphnia magna*	S, M	Zinc chloride	54	334	-	Chapman, et al. Manuscript
Cladoceran, *Daphnia magna*	S, M	Zinc chloride	105	525	-	Chapman, et al. Manuscript
Cladoceran, *Daphnia magna*	S, M	Zinc chloride	196	655	-	Chapman, et al. Manuscript
Cladoceran, *Daphnia pulex*	S, M	Zinc sulfate	45	500	-	Cairns, et al. 1978
Scud, *Gammarus* sp.	S, M	-	50	8,100	-	Rehwoldt, et al. 1973
Damselfly, Unidentified sp.	S, M	-	50	26,200	-	Rehwoldt, et al. 1973
Midge, *Chironomus* sp.	S, M	-	50	18,200	-	Rehwoldt, et al. 1973

Table 1. (Continued)

Species	Method*	Chemical	Hardness (mg/l as $CaCO_3$)	LC50/EC50** (µg/l)	Species Mean Acute Values** (µg/l)	Reference
Caddisfly, Unidentified sp.	S, M	-	50	58,100	-	Rehwoldt, et al. 1973
Rotifer, *Philodia acuticornis*	S, U	Zinc chloride	25	1,500	-	Buikema, et al. 1974
Rotifer, *Philodia acuticornis*	S, U	Zinc sulfate	25	1,200	-	Buikema, et al. 1974
American eel, *Anguilla rostrata*	S, m	Zinc nitrate	53	14,600	-	Rehwoldt, et al. 1971
American eel, *Anguilla rostrata*	S, M	-	55	14,500	-	Rehwoldt, et al. 1972
Coho salmon, *Oncorhynchus kisutch*	FT, M	Zinc chloride	25	905	-	Chapman & Stevens, 1978
Coho salmon, *Oncorhynchus kisutch*	FT, M	Zinc chloride	94	4,600	-	Lorz & McPherson, 1976
Sockeye salmon *Oncorhynchus nerka*	FT, M	Zinc chloride	22	749	-	Chapman, 1978a
Chinook salmon (swimup), *Oncorhynchus tshawytscha*	FT, M	Zinc chloride	24	97	-	Chapman, 1978b
Chinook salmon (parr), *Oncorhynchus tshawytscha*	FT, M	Zinc chloride	22	463	-	Chapman, 1978b
Chinook salmon (smolt), *Oncorhynchus tshawytscha*	FT, M	Zinc chloride	24	701	-	Chapman, 1978b
Cutthroat trout, *Salmo clarki*	R, M	Zinc sulfate	-	90	-	Rabe & Sappington, 1970
Rainbow trout (alevin), *Salmo gairdneri*	FT, M	Zinc chloride	22	815	-	Chapman, 1978b
Rainbow trout (swimup) *Salmo gairdneri*	FT, M	Zinc chloride	22	93	-	Chapman, 1978b

Table 1. (Continued)

Species	Method*	Chemical	Hardness (mg/l as $CaCO_3$)	LC50/EC50** (µg/l)	Specues Mean Acute Value** (µg/l)	Reference
Rainbow trout (parr), *Salmo gairdneri*	FT, M	Zinc chloride	24	136	-	Chapman, 1978b
Rainbow trout, *Salmo gairdneri*	FT, M	Zinc chloride	83	1,760	-	Chapman & Stevens, 1978
Rainbow trout, *Salmo gairdneri*	R, U	Zinc phosphate	20	90	-	Garton, 1972
Rainbow trout, *Salmo gairdneri*	FT, M	Zinc sulfate	350	4,520	-	Goettl, et al. 1972
Rainbow trout, *Salmo gairdneri*	FT, M	Zinc sulfate	350	1,190	-	Goettl, et al. 1972
Rainbow trout, *Salmo gairdneri*	FT, M	Zinc sulfate	30	560	-	Goettl, et al. 1972
Rainbow trout, *Salmo gairdneri*	FT, M	Zinc sulfate	30	240	-	Goettl, et al. 1972
Rainbow trout, *Salmo gairdneri*	FT, M	Zinc sulfate	30	810	-	Goettl, et al. 1972
Rainbow trout, *Salmo gairdneri*	FT, M	Zinc sulfate	30	410	-	Goettl, et al. 1972
Rainbow trout, *Salmo gairdneri*	FT, M	Zinc sulfate	30	830	-	Goettl, et al. 1972
Rainbow trout, *Salmo gairdneri*	FT, M	Zinc sulfate	47	370	-	Holcombe & Andrew, 1978
Rainbow trout, *Salmo gairdneri*	FT, M	Zinc sulfate	47	517	-	Holcombe & Andrew, 1978
Rainbow trout, *Salmo gairdneri*	FT, M	Zinc sulfate	44	756	-	Holcombe & Andrew, 1978
Rainbow trout, *Salmo gairdneri*	FT, M	Zinc sulfate	178	2,510	-	Holcombe & Andrew, 1978

Table I. (Continued)

Species	Method*	Chemical	Hardness (mg/l as $CaCO_3$)	LC50/EC50** (µg/l)	Species Mean Acute Value** (µg/l)	Reference
Rainbow trout, *Salmo gairdneri*	FT, M	Zinc sulfate	179	2,960	-	Holcombe & Andrew, 1978
Rainbow trout, *Salmo gairdneri*	FT, M	Zinc sulfate	170	1,910	-	Holcombe & Andrew, 1978
Rainbow trout, *Salmo gairdneri*	R, U	Zinc sulfate	5	280	-	McLeay, 1976
Rainbow trout, *Salmo gairdneri*	FT, M	Zinc sulfate	333	7,210	-	Sinley, et al. 1974
Rainbow trout, *Salmo gairdneri*	FT, M	Zinc sulfate	26	430	-	Sinley, et al. 1974
Rainbow trout, *Salmo gairdneri*	FT, M	Zinc sulfate	500	4,700	-	Solbe, 1974
Atlantic salmon, *Salmo salar*	FT, M	Zinc sulfate	14	740	-	Carson & Carson, 1972
Atlantic salmon, *Salmo salar*	FT, M	Zinc sulfate	20	600	-	Sprague, 1964a
Atlantic salmon, *Salmo salar*	FT, M	-	14	420	-	Sprague & Ramsey, 1965
Brook trout, *Salvelinus fontinalis*	FT, M	Zinc sulfate	47	1,550	-	Holcombe & Andrew, 1978
Brook trout, *Salvelinus fontinalis*	FT, M	Zinc sulfate	47	2,120	-	Holcombe & Andrew, 1978
Brook trout, *Salvelinus fontinalis*	FT, M	Zinc sulfate	44	2,420	-	Holcombe & Andrew, 1978
Brook trout, *Salvelinus fontinalis*	FT, M	Zinc sulfate	178	6,140	-	Holcombe & Andrew, 1978
Brook trout, *Salvelinus fontinalis*	FT, M	Zinc sulfate	179	6,980	-	Holcombe & Andrew, 1978

Table 1. (Continued)

Species	Method*	Chemical	Hardness (mg/l as $CaCO_3$)	LC50/EC50** (µg/l)	Species Mean Acute Value** (µg/l)	Reference
Brook trout, *Salvelinus fontinalis*	FT, M	Zinc sulfate	170	4,980	-	Holcombe & Andrew, 1978
Longfin dace, *Agosia chrysogaster*	R, M	Zinc sulfate	217	790	-	Lewis, 1978
Goldfish, *Carassius auratus*	S, U	Zinc sulfate	20	6,440	-	Pickering & Henderson, 1966
Goldfish, *Carassius auratus*	S, U	Zinc sulfate	45	7,500	-	Cairns, et al. 1969
Carp, *Cyprinus carpio*	S, M	Zinc nitrate	53	7,800	-	Rehwoldt, et al. 1971
Carp, *Cyprinus carpio*	S, M	-	55	7,800	-	Rehwoldt, et al. 1972
Golden shiner, *Notemigonus crysoleucus*	S, U	Zinc sulfate	45	6,000	-	Cairns, et al. 1969
Fathead minnow, *Pimephales promelas*	FT, M	Zinc sulfate	46	600	-	Benoit & Holcombe, 1978
Fathead minnow, *Pimephales promelas*	FT, M	Zinc sulfate	200	2,610	-	Broderius & Smith, 1979
Fathead minnow, *Pimephales promelas*	FT, M	Zinc sulfate	203	8,400	-	Brungs, 1969
Fathead minnow, *Pimephales promelas*	FT, M	Zinc sulfate	203	10,000	-	Brungs, 1969
Fathead minnow, *Pimephales promelas*	S, U	Zinc sulfate	203	12,000	-	Brungs, 1969
Fathead minnow, *Pimephales promelas*	S, U	Zinc sulfate	203	13,000	-	Brungs, 1969
Fathead minnow, *Pimephales promelas*	S, M	Zinc sulfate	45	3,100	-	Judy & Davies, 1979

Table 1. (Continued)

Species	Method*	Chemical	Hardness (mg/l as $CaCO_3$)	LC50/EC50** (µg/l)	Species Mean Acute Value** (µg/l)	Reference
Fathead minnow, *Pimephales promelas*	FT, M	Zinc sulfate	50	12,500	-	Mount, 1966
Fathead minnow, *Pimephales promelas*	FT, M	Zinc sulfate	50	13,800	-	Mount, 1966
Fathead minnow, *Pimephales promelas*	FT, M	Zinc sulfate	100	18,500	-	Mount, 1966
Fathead minnow, *Pimephales promelas*	FT, M	Zinc sulfate	100	25,000	-	Mount, 1966
Fathead minnow, *Pimephales promelas*	FT, M	Zinc sulfate	200	29,000	-	Mount, 1966
Fathead minnow, *Pimephales promelas*	FT, M	Zinc sulfate	200	35,500	-	Mount, 1966
Fathead minnow, *Pimephales promelas*	FT, M	Zinc sulfate	50	13,700	-	Mount, 1966
Fathead minnow, *Pimephales promelas*	FT, M	Zinc sulfate	50	6,200	-	Mount, 1966
Fathead minnow, *Pimephales promelas*	FT, M	Zinc sulfate	100	12,500	-	Mount, 1966
Fathead minnow, *Pimephales promelas*	FT, M	Zinc sulfate	100	12,500	-	Mount, 1966
Fathead minnow, *Pimephales promelas*	FT, M	Zinc sulfate	200	19,000	-	Mount, 1966
Fathead minnow, *Pimephales promelas*	FT, M	Zinc sulfate	200	13,600	-	Mount, 1966
Fathead minnow, *Pimephales promelas*	FT, M	Zinc sulfate	50	4,700	-	Mount, 1966
Fathead minnow, *Pimephales promelas*	FT, M	Zinc sulfate	50	5,100	-	Mount, 1966

Table 1. (Continued)

Species	Method*	Chemical	Hardness (mg/l as $CaCO_3$)	LC50/EC50** (µg/l)	Species Mean Acute Value** (µg/l)	Reference
Fathead minnow, *Pimephales promelas*	FT, M	Zinc sulfate	100	8,100	-	Mount, 1966
Fathead minnow, *Pimephales promelas*	FT, M	Zinc sulfate	100	9,900	-	Mount, 1966
Fathead minnow, *Pimephales promelas*	FT, M	Zinc sulfate	200	8,200	-	Mount, 1966
Fathead minnow, *Pimephales promelas*	FT, M	Zinc sulfate	200	15,500	-	Mount, 1966
Fathead minnow, *Pimephales promelas*	S, U	Zinc sulfate	20	960	-	Pickering & Henderson, 1966
Fathead minnow, *Pimephales promelas*	S, U	Zinc sulfate	20	780	-	Pickering & Henderson, 1966
Fathead minnow, *Pimephales promelas*	S, U	Zinc sulfate	360	33,400	-	Pickering & Henderson, 1966
Fathead minnow, *Pimephales promelas*	S, U	-	20	2,550	-	Pickering & Henderson, 1966
Fathead minnow, *Pimephales promelas*	S, U	-	20	2,330	-	Pickering & Henderson, 1966
Fathead minnow (fry), *Pimephales promelas*	FT, M	Zinc sulfate	186	870	-	Pickering and Vigor, 1965
Fathead minnow, *Pimephales promelas*	S, U	Zinc sulfate	166	7,630	-	Rachlin & Perlmutter, 1968
Banded killifish, *Fundulus diaphanus*	S, M	-	55	19,200	-	Rehwoldt, et al. 1972
Banded killifish, *Fundulus diaphanus*	S, M	-	53	19,100	-	Rehwoldt, et al. 1971

Table 1. (Continued)

Species	Method*	Chemical	Hardness (mg/l as $CaCO_3$)	LC50/EC50** (µg/l)	Species Mean Acute Value** (µg/l)	Reference
Flagfish, *Jordanella floridae*	FT, M	Zinc sulfate	44	1,500	-	Spehar, 1976
Guppy, *Poecilia reticulata*	S, U	Zinc sulfate	45	30,000	-	Cairns, et al. 1969
Guppy, *Poecilia reticulata*	S, U	Zinc sulfate	20	1,270	-	Pickering & Henderson, 1966
Southern platyfish, *Xiphophorus maculatus*	S, U	Zinc sulfate	166	12,000	-	Rachlin & Perlmutter, 1968
White perch, *Morone americana*	S, M	Zinc nitrate	53	14,300	-	Rehwoldt, et al. 1971
White perch, *Morone americana*	S, M	-	55	14,400	-	Rehwoldt, et al. 1972
Striped bass, *Morone saxatilis*	S, M	-	55	6,800	-	Rehwoldt, et al. 1972
Striped bass, *Morone saxatilis*	S, M	Zinc nitrate	53	6,700	-	Rehwoldt, et al. 1971
Striped bass (fry), *Morone saxatilis*	S, M	-	137	1,180	-	O'Rear, 1972
Striped bass (larvae), *Morone saxatilis*	S, U	Zinc chloride	38	100	-	Hughes, 1973
Pumpkinseed, *Lepomis gibbosus*	S, M	Zinc nitrate	53	20,000	-	Rehwoldt, et al. 1971
Pumpkinseed, *Lepomis gibbosus*	S, M	-	55	20,100	-	Rehwoldt, et al. 1972
Bluegill, *Lepomis macrochirus*	FT, M	Zinc sulfate	46	9,900	-	Cairns, et al. 1971
Bluegill, *Lepomis macrochirus*	FT, M	Zinc sulfate	46	12,100	-	Cairns, et al. 1971

Table 1. (Continued)

Species	Method*	Chemical	Hardness (mg/l as $CaCO_3$)	LC50/EC50** (µg/l)	Species Mean Acute Value** (µg/l)	Reference
Bluegill, *Lepomis macrochirus*	S, U	Zinc chloride	52	7,450	-	Cairns & Scheier, 1959
Bluegill, *Lepomis macrochirus*	S, U	Zinc chloride	52	7,200	-	Cairns and Scheier, 1959
Bluegill, *Lepomis macrochirus*	S, U	Zinc chloride	52	6,910	-	Cairns & Scheier, 1959
Bluegill, *Lepomis macrochirus*	S, U	Zinc sulfate	20	5,460	-	Pickering & Henderson, 1966
Bluegill, *Lepomis macrochirus*	S, U	Zinc sulfate	20	4,850	-	Pickering & Henderson, 1966
Bluegill, *Lepomis macrochirus*	S, U	Zinc sulfate	20	5,820	-	Pickering & Henderson, 1966
Bluegill, *Lepomis macrochirus*	S, U	Zinc chloride	20	5,370	-	Pickering & Henderson, 1966
Bluegill, *Lepomis macrochirus*	S, U	Zinc sulfate	360	40,900	-	Pickering & Henderson, 1966
Bluegill, *Lepomis macrochirus*	S, U	-	20	6,440	-	Pickering & Henderson, 1966
Bluegill, *Lepomis macrochirus*	S, U	Zinc chloride	45	3,840	-	Cairns & Scheier, 1957a
Bluegill, *Lepomis macrochirus*	S, M	Zinc chloride	45	3,750***	-	Cairns & Scheier, 1957b
Bluegill, *Lepomis macrochirus*	S, M	Zinc chloride	45	3,430***	-	Cairns & Scheier, 1957b
Bluegill, *Lepomis macrochirus*	S, M	Zinc chloride	174	12,390***	-	Cairns & Scheier, 1957b

Table 1. (Continued)

Species	Method*	Chemical	Hardness (mg/l as $CaCO_3$)	LC50/EC50** (µg/l)	Species Mean Acute Value** (µg/l)	Reference
Bluegill, *Lepomis macrochirus*	S,M	Zinc chloride	174	12,120***	-	Cairns & Scheier, 1957b
			SALTWATER SPECIES			
Polychaete (adult), *Capitella capitata*	S, U	Zinc sulfate	-	3,500	-	Reish, et al. 1976
Polychaete (larvae), *Capitella capitata*	S, U	Zinc sulfate	-	1,700	2,440	Reish, et al. 1976
Polychaete (adult), *Neanthes arenaceodentata*	S, U	Zinc sulfate	-	1,800	-	Reish, et al. 1976
Polychaete (juveniles), *Neanthes arenaceodentata*	S, U	Zinc sulfate	-	900	1,270	Reish, et al. 1976
Polychaete (adult), *Nereis diversicolor*	S, U	Zinc sulfate	-	55,000	-	Bryan & Hummerstone, 1973
Polychaete (adult), *Nereis diversicolor*	S, U	Zinc sulfate	-	11,000	24,600	Bryan & Hummerstone, 1973
Sandworm (adult), *Nereis virens*	S, U	Zinc chloride	-	8,100	8,100	Eisler & Hennekey, 1977
Oyster, *Crassostrea virginica*	S, U	Zinc chloride	-	310	310	Calabrese, et al. 1973
Hard shelled clam, *Mercenaria mercenaria*	S, U	Zinc chloride	-	166	166	Calabrese & Nelson, 1974
Soft shelled clam, *Mya arenaria*	S, U	Zinc chloride	-	5,200	-	Eisler, 1977a
Soft shelled clam, *Mya arenaria*	S, U	Zinc chloride	-	7,700	6,330	Eisler & Hennekey, 1977

Table 1. (Continued)

Species	Method*	Chemical	Hardness (mg/l as $CaCO_3$)	LC50/EC50 (µg/l)**	Species Mean Acute Value** (µg/l)	Reference
Mussel, *Mytilus edulis planulatus*	F, M	Zinc chloride	-	4,300	-	Ahsanullah, 1976
Mussel, *Mytilus edulis planulatus*	F, M	Zinc chloride	-	3,600	-	Ahsanullah, 1976
Mussel, *Mytilus edulis planulatus*	S, M	Zinc chloride	-	2,500	3,380	Ahsanullah, 1976
Mud snail (adult), *Nassarius obsoletus*	S, U	Zinc chloride	-	50,000	50,000	Eisler & Hennekey, 1977
Copepod (adult) *Acartia clausi*	S, U	Zinc chloride	-	950	950	U.S. EPA, 1980
Copepod (adult), *Acartia tonsa*	S, U	Zinc chloride	-	290	290	U.S. EPA, 1980
Copepod (adult), *Eurytemora affinis*	S, U	Zinc chloride	-	4,090	4,090	U.S. EPA, 1980
Copepod (adult), *Nitocra spinipes*	S, U	Zinc chloride	-	1,450	1,450	Bengtsson, 1978
Copepod (adult), *Pseudodiaptomus coronatus*	S, U	Zinc chloride	-	1,783	1,780	U.S. EPA, 1980
Copepod (adult), *Tigriopus japonicus*	S, U	Zinc chloride	-	2,160	2,160	U.S. EPA, 1980
Mysid shrimp, *Mysidopsis bahia*	S, M	Zinc chloride	-	498	498	U.S. EPA, 1980
Mysid shrimp, *Mysidopsis bigelowi*	S, M	Zinc chloride	-	591	591	U.S. EPA, 1980
Lobster (larvae), *Homarus americanus*	S, U	Zinc chloride	-	575	-	U.S. EPA, 1980
Lobster (larvae), *Homarus americanus*	S, U	Zinc chloride	-	375	-	U.S. EPA, 1980

Table 1. (Continued)

Species	Method*	Chemical	Hardness (mg/l as $CaCO_3$)	LC50/EC50 (µg/l)**	Species Mean Acute Value** (µg/l)	Reference
Lobster (larvae), *Homarus americanus*	S, U	Zinc chloride	-	282	-	U.S. EPA, 1980
Lobster (larvae), *Homarus americanus*	S, U	Zinc chloride	-	175	321	U.S. EPA, 1980
Crab (larvae), *Carcinus maenas*	S, U	Zinc sulfate	-	1,000	1,000	Conner, 1972
Hermit crab (adult), *Pagurus longicarpus*	S, U	Zinc chloride	-	400	400	Eisler & Hennekey, 1977
Starfish (adult), *Asterias forbesi*	S, U	Zinc chloride	-	39,000	39,000	Eisler & Hennekey, 1977
Mummichog (adult), *Fundulus heteroclitus*	S, U	Zinc chloride	-	60,000	-	Eisler & Hennekey, 1977
Mummichog (larvae), *Fundulus heteroclitus*	S, U	Zinc chloride	-	83,000	70,600	U.S. EPA, 1980
Atlantic silverside (larvae), *Menidia menidia*	S, U	Zinc chloride	-	4,960	-	U.S. EPA, 1980
Atlantic silverside (larvae), *Menidia menidia*	S, U	Zinc chloride	-	4,170	-	U.S. EPA, 1980
Atlantic silverside (larvae), *Menidia menidia*	S, U	Zinc chloride	-	3,700	-	U.S. EPA, 1980
Atlantic silverside (larvae), *Menidia menidia*	S, U	Zinc chloride	-	3,060	-	U.S. EPA, 1980
Atlantic silverside (larvae), *Menidia menidia*	S, U	Zinc chloride	-	2,730	3,640	U.S. EPA, 1980
Winter flounder (larvae), *Pseudopleuronectes americanus*	S, U	Zinc chloride	-	18,200	-	U.S. EPA, 1980

Table 1. (Continued)

Species	Method*	Chemical	Hardness (mg/l as $CaCO_3$)	LC50/EC50 (µg/l)**	Species Mean Acute Value** (µg/l)	Reference
Winter flounder (larvae), Pseudopleuronectes americanus	S, U	Zinc chloride	-	4,920	9,460	U.S. EPA, 1980

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*   S = static; FT = flow-through; R = renewal; M = measured; U = unmeasured

** Results are expressed as zinc, not as the compound.

***Calculated by logit analysis of the authors' data.

Species	N	Slope	Intercept	R	Significance
Snail, Physa heterostropha	4	1.18	2.19	0.99	*
Cladoceran, Daphnia magna	5	0.90	1.87	0.80	N.S.
Coho salmon, Oncorhynchus kisutch	2	1.23	2.86	-	-
Rainbow trout, Salmo gairdneri	22	0.85	3.18	0.83	**
Brook trout, Salvelinus fontinalis	6	0.82	4.48	0.96	**
Goldfish, Carassius auratus	2	0.19	8.20	-	-
Fathead minnow, Pimephales promelas	32	0.78	5.35	0.60	**
Guppy, Poecilia reticulata	2	3.90	-4.53	-	-
Striped bass, Morone saxatilis	4	0.79	4.05	0.22	N.S.

Table 1. (Continued)

Species	N	Slope	Intercept	R	Significance
Bluegill, *Lepomis macrochirus*	16	0.54	6.80	0.76	**

* = significant at p = 0.05

** = significant at p = 0.01

Arithmetic mean acute slope = 0.83 (n = 5, see text)

Table 2. Chronic values for zinc

Species	Test*	Chemical	Hardness (mg/l as $CaCO_3$)	Limits** (µg/l)	Chronic Value** (µg/l)	Reference
FRESHWATER SPECIES						
Cladoceran *Daphnia magna*	LC	Zinc chloride	45	70-102	85	Biesinger & Christensen, 1972
Cladoceran, *Daphnia magna*	LC	Zinc chloride	52	97-190	136	Chapman, et al. Manuscript
Cladoceran, *Daphnia magna*	LC	Zinc chloride	104	43-52	47	Chapman, et al. Manuscript
Cladoceran, *Daphnia magna*	LC	Zinc chloride	211	42-52	47	Chapman, et al. Manuscript
Chinook salmon, *Oncorhynchus tshawytscha*	ELS	Zinc chloride	25	270-510	371	Chapman, Manuscript
Rainbow trout, *Salmo gairdneri*	ELS	Zinc sulfate	26	140-547	277	Sinley, et al. 1974
Brook trout, *Salvelinus fontinalis*	LC	Zinc sulfate	45	534-1,360	852	Holcombe, et al. 1979
Fathead minnow, *Pimephales promelas*	LC	Zinc sulfate	46	78-145	106	Benoit & Holcombe, 1978
Flagfish, *Jordanella floridae*	LC	Zinc sulfate	44	26-85	47	Spehar, 1976
SALTWATER SPECIES						
Mysid shrimp, *Mysidopsis bahia*	LC	Zinc chloride	-	120-231	166	U.S. EPA, 1980

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* LC = life cycle or partial life cycle; ELS = early life stage

** Results are expressed as zinc, not as the chemical.

Table 2. (Continued)

Species	Hardness (mg/l as $CaCO_3$)	Acute Value (µg/l)	Chronic Value (µg/l)	Ratio
	Acute-Chronic Ratio			
Cladoceran, *Daphnia magna*	45	100	85	1.2
Cladoceran, *Daphnia magna*	52-54	334	136	2.4
Cladoceran, *Daphnia magna*	104-105	525	47	11
Cladoceran, *Daphnia magna*	196-211	655	47	14
Chinook salmon, *Oncorhynchus tshawytscha*	22-25	97-701	371	0.26-1.89
Rainbow trout, *Salmo gairdneri*	26-30	240-830*	277	0.87-3.0
Brook trout, *Salvelinus fontinalis*	45	2,000	852	2.3
Fathead minnow, *Pimephales promelas*	46	600	106	5.7
Flagfish, *Jordanella floridae*	44	1,500	47	32
Mysid shrimp, *Mysidopsis bahia*	-	498	166	3.0

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* Acute values from Goettl et al. 1972.

Final Acute-Chronic Ratio = 3.0 (see text)

Table 3. Species mean acute intercepts and values and acute-chronic ratos for zinc

Rank*	Species	Species Mean Acute Intercept (µg/l)	Species Mean Acute-Chronic Ratio
		FRESHWATER SPECIES	
29	Caddisfly, Unidentified sp.	2,260	-
28	Damselfly, unidentified sp.	1,019	-
27	Pumpkinseed, *Lepomis gibbosus*	732	-
26	Worm, *Nais* sp.	716	-
25	Midge, *Chironomus* sp.	708	-
24	Banded killifish, *Fundulus diaphanus*	699	-
23	American eel, *Anguilla rostrata*	531	-
22	White perch, *Morone americana*	524	-
21	Goldfish, *Carassius auratus*	413	-
20	Guppy, *Poecilia reticulata*	367	-
19	Scud, *Gammarus* sp.	315	-
18	Bluegill, *Lepomis macrochirus*	293	-
17	Carp, *Cyprinus carpio*	285	-
16	Golden shiner, *Notemigonus crysoleucus*	255	-

Table 3. (Continued)

Rank*	Species	Species Mean Acute Intercept (µg/l)	Species Mean Acute-Chronic Ratio
15	Southern platyfish, *Xiphophorus maculatus*	172	-
14	Fathead minnow, *Pimephales promelas*	169	5.7
13	Rotifer, *Philodia acuticornis*	92.8	-
12	Brook trout, *Salvelinus fontinalis*	82.6	2.3
11	Coho salmon, *Oncorhynchus kisutch*	81.4	-
10	Flagfish, *Jordanella floridae*	64.9	32
9	Atlantic salmon, *Salmo salar*	57.9	-
8	Sockeye salmon, *Oncorhynchus nerka*	57.6	-
7	Striped bass, *Morone saxatilis*	49.3	-
6	Snail, *Physa heterostropha*	42.0	-
5	Rainbow trout, *Salmo gairdneri*	26.2	0.87-3.0
4	Chinook salmon, *Oncorhynchus tshawytscha*	23.1	0.26-1.89
3	Cladoceran, *Daphnia pulex*	21.2	-
2	Longfin dace, *Agosia chrysogaster*	9.09	-

Table 3. (Continued)

Rank*	Species	Species Mean Acute Intercept (µg/l)	Species Mean Acute-Chronic Ratio
1	Cladoceran, *Daphnia magna*	8.89	1.2-14

Rank*	Species	Species Mean Acute Value (µg/l)	Species Mean Acute-Chronic Ratio
		SALTWATER SPECIES	
24	Mummichog, *Fundulus heteroclitus*	70,600	-
23	Mud snail, *Nassarius obsoletus*	50,000	-
22	Starfish, *Asterias forbesi*	39,000	-
21	Polychaete, *Nereis diverscolor*	24,600	-
20	Winter flounder, *Pseudopleuronectes americanus*	9,460	
19	Sandworm, *Nereis virens*	8,100	-
18	Soft shelled clam, *Mya arenaria*	6,330	-
17	Copepod, *Eurytemora affinis*	4,090	-
16	Atlantic silverside *Menidia menidia*	3,640	-
15	Mussel, *Mytilus edulis planulatus*	3,380	-
14	Polychaete, *Capitella capitata*	2,440	-

Table 3. (continued)

Rank*	Species	Species Mean Acute Value (µg/l)	Species Mean Acute-Chronic Ratio
13	Copepod, *Tigriopus japonicus*	2,160	-
12	Copepod, *Pseudodiaptomus coronatus*	1,780	-
11	Copepod, *Nitocra spinipes*	1,450	-
10	Polychaete, *Neanthes arenaceodentata*	1,270	-
9	Crab, *Carcinus naenas*	1,000	-
8	Copepod, *Acartia clausi*	950	-
7	Mysid shrimp *Mysidopsis bigelowi*	591	-
6	Mysid shrimp, *Mysidopsis bahia*	498	3.0
5	Hermit crab, *Pagurus longicarpus*	400	-
4	Lobster, *Homarus americanus*	321	-
3	Oyster, *Crassostrea virginica*	310	-
2	Copepod, *Acartia tonsa*	290	-
1	Hard shelled clam, *Mercenaria mercenaria*	166	-

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* Ranked from least sensitive to most sensitive based on species mean acute intercept or value.

Table 3. (continued)

Freshwater:

Final Acute Intercept = 7.02 µg/l

Natural logarithm of 7.02 = 1.95

Acute slope = 0.83

Final Acute Equation = $e^{(0.83[\ln(\text{hardness})]+1.95)}$

Final Acute-Chronic Ratio = 3.0 (Table 2)

Final Chronic Intercept = (7.02 µg/l)/3.0 = 2.34 µg/l

Natural logarithm of 2.34 = 0.85

Chronic slope = 0.83

Final Chronic Equation = $e^{(0.83[\ln(\text{hardness})]+0.85)}$

Final Chronic Value = 47 µg/l (see text)

Saltwater:

Final Acute Value = 173 µg/l

Final Acute-Chronic Ratio = 3.0 (Table 2)

Final Chronic Value = (173 µg/l)/3.0 = 57.7 µg/l

Table 4. Plant values for zinc

Species	Chemical	Hardness (mg/l as $CaCO_3$)	Effect	Result* (µg/l)	Reference
		FRESHWATER SPECIES			
Alga, *Chorella vulgaris*	Zinc chloride	-	33-day EC50 cell number	5,100	Rosko & Rachlin, 1977
Alga, *Chorella vulgaris*	Zinc chloride	-	96-hour EC50 growth	2,400	Rachlin & Farran, 1974
Alga, *Selenastrum capricornutum*	Zinc chloride	-	7-day LC100	700	Bartlett, et al. 1974
Alga, *Selenastrum capricornutum*	Zinc chloride	-	7-day EC100 growth	120	Bartlett, et al. 1974
Alga, *Selenastrum capricornutum*	Zinc chloride	-	7-day incipient growth inhibition	30	Bartlett, et al. 1974
Alga, *Selenastrum capricornutum*	Zinc chloride	-	14-day EC95 growth	40	Greene, et al. 1975
Alga, *Selenastrum capricornutum*	Zinc chloride	-	14-day EC95 growth	68	Greene, et al. 1975
Alga, *Chlamydomonas* sp.	Zinc sulfate	-	5-day EC65 mean growth rate	15,000	Cairns, et al. 1978
Alga, *Scenedesmus quadricauda*	Zinc sulfate	-	5-day EC25 mean growth rate	20,000	Cairns, et al. 1978
Alga, *Cyclotella meneghiniana*	Zinc sulfate	-	5-day EC65 mean growth rate	20,000	Cairns, et al. 1978
Diatom, *Nitzschia linearis*	Zinc chloride	-	12-hr LC50	4,300	Patrick, et al. 1968
Eurasian watermilfoil, *Myriophyllum spicatum*	-	-	32-day EC50 root weight	21,600	Stanley, 1974
Eurasian watermilfoil, *Myriophyllum spicatum*	-	-	32-day EC50 root length	21,600	Stanley, 1974
Eurasian watermilfoil, *Myriophyllum spicatum*	-	-	32-day EC50 shoot length	20,900	Stanley, 1974

Table 4. (continued)

Species	Chemical	Hardness (mg/l as $CaCO_3$)	Effect	Result* (µg/l)	Reference
Duckweed, *Lemna minor*	Zinc sulfate	-	28-day LC50	67,700	Brown & Rattigan, 1979
Macrophyte, *Elodea canadensis*	Zinc sulfate	-	28-day LC50	22,500	Brown & Rattigan, 1979
Macrophyte, *Elodea canadensis*	Zinc sulfate	-	28-day EC50 photosynthesis	8,100	Brown & Rattigan, 1979
		SALTWATER SPECIES			
Alga,, *Amphidinium carteri*	Zinc sulfate	-	Growth inhibition	400	Braek, et al. 1976
Alga,, *Amphidinium carteri*	Zinc sulfate	-	Interaction with copper on growth	100	Braek, et al. 1976
Alga, *Dunaliella tertiolecta*	-	-	Reduction in potassium content	6,500	Overnell, 1975
Kelp, *Laminaria hyperiborea*	Zinc sulfate	-	Growth inhibition	250	Hopkins & Kain, 1971
Kelp, *Laminaria digitata*	Zinc sulfate	-	Growth inhibition	100	Bryan, 1969
Giant kelp, *Macrocystis pyrifera*	-	-	50% inhibition of photosynthesis	10,000	Clendenning & North, 1959
Alga, *Phaeodactylum tricornutum*	Zinc chloride	-	Growth inhibition	25,000	Jensen, et al. 1974
Alga, *Phaeodactylum tricornutum*	Zinc sulfate	-	Interaction with copper on growth	1,000	Braek, et al. 1976
Alga, *Skeletonema costatum*	Zinc sulfate	-	Growth inhibition	200	Braek, et al. 1976
Alga, *Skeletonema costatum*	Zinc sulfate	-	Interaction with copper on growth	50	Braek, et al. 1976

Table 4. (continued)

Species	Chemical	Hardness (mg/l as $CaCO_3$)	Effect	Result* (µg/l)	Reference
Algae, *Thalassiosira pseudonana*	Zinc sulfate	-	Growth inhibition	400	Braek, et al., 1976
Alga, *Thalassiosira pseudonana*	Zinc sulfate	-	Interaction with copper on growth	200	Braek, et al. 1976
Alga, *Scrippsiella faeroense*	Zinc sulfate	-	Decrease in cell numbers	1,000	Kayser, 1977
Alga, *Procentium micans*	Zinc sulfate	-	Decrease in cell numbers	500	Kayser, 1977
Alga, *Gymnodinium splendens*	Zinc sulfate	-	Decrease in cell numbers	100	Kayser, 1977
Alga, *Schroederella schroederi*	Zinc sulfate	-	Decrease in cell numbers	50	Kayser, 1977
Alga, *Thalassiosira rotula*	Zinc sulfate	-	Decrease in cell numbers	100	Kayser, 1977

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* Results are expressed as zinc, not as the compound.

Table 5. Residues for zinc

Species	Tissue	Chemical	Hardness (mg/l as $CaCO_3$)	Bioconcentration factor	Duration (days)	Reference
			FRESHWATER SPECIES			
Mayfly, *Ephemerella grandis*	Whole body	Zinc sulfate	30-70	1,130	14	Nehring, 1976
Stonefly, *Pteronarcys californica*	Whole body	Zinc sulfate	30-70	107	14	Nehring, 1976
Atlantic salmon, *Salmo salar*	Whole body	Zinc sulfate	12-24	51	80	Farmer, et al. 1979
Flagfish, *Jordanella floridae*	Whole body	Zinc sulfate	44	432	100	Spehar, et al. 1978
			SALTWATER SPECIES			
Alga, *Cladophora* sp.	-	Zinc chloride	-	4,680	34	Baudin, 1974
Alga, *Fucus serratus*	-	Zinc chloride	-	16,600	140	Young, 1975
Alga, *Enteromorpha prolifera*	-	Zinc sulfate	-	1,530	12	Munda, 1979
Polychaete (adult), *Nereis diversicolor*	-	Zinc sulfate	-	20	34	Bryan & Hummerstone, 1973
Oyster (adult), *Crassostrea virginica*	-	Zinc chloride	-	16,700	140	Shuster & Pringle, 1969
Gastropod (adult), *Littorina obtusata*	-	Zinc chloride	-	670	50	Young, 1975
Soft-shell clam (adult), *Mya arenaria*	Soft parts	Zinc chloride	-	85	50	Pringle, et al. 1968
Soft-shell clam (adult), *Mya arenaria*	Soft parts	Zinc chloride	-	43	112	Eisler, 1977b
Mussel (adult), *Mytilus edulis*	Soft parts	Zinc chloride	-	225	13	Phillips, 1977

Table 5. (Continued)

Species	Tissue	Chemical	Hardness (mg/l as $CaCO_3$)	Bioconcentration factor	Duration (days)	Reference
Mussel (adult), *Mytilus edulis*	Soft parts	Zinc chloride	-	500	21	Pentreath, 1973
Mussel (adult), *Mytilus edulis*	Soft parts	Zinc chloride	-	282	35	Phillips, 1976
Crab (adult), *Carcinus maenas*	Muscle	Zinc chloride	-	8,800	22	Bryan, 1966

Table 6. Other data for zinc

Species	Chemical	Hardness (mg/l as $CaCO_3$)	Duration	Effect	Result* (µg/l)	Reference
		FRESHWATER SPECIES				
Algae, *Selenastrum capricornutum*	Zinc phosphate	15	14 days	Growth inhibition	64	Garton, 1972
Cladoceran, *Daphnia magna*	Zinc chloride	-	64 hrs	LC50	72	Anderson, 1948
Snail, *Gonobasis livescens*	Zinc sulfate	154	48 hrs	LC50	13,500	Cairns, et al. 1976
Snail, *Lymnaea emarginata*	Zinc sulfate	154	48 hrs	LC50	4,150	Cairns, et al. 1976
Snail, *Physa integra*	Zinc sulfate	154	48 hrs	LC50	4,400	Cairns, et al. 1976
Cladoceran, *Daphnia magna*	Zinc sulfate	45	48 hrs	LC50 (5 C)	2,300	Cairns, et al. 1978
Cladoceran, *Daphnia magna*	Zinc sulfate	45	48 hrs	LC50 (10 C)	1,700	Cairns, et al. 1978
Cladoceran, *Daphnia magna*	Zinc sulfate	45	48 hrs	LC50 (15 C)	1,100	Cairns, et al. 1978
Cladoceran, *Daphnia magna*	Zinc sulfate	45	48 hrs	LC50 (25 C)	560	Cairns, et al. 1978
Cladoceran, *Daphnia pulex*	Zinc sulfate	45	48 hrs	LC50 (5 C)	1,600	Cairns, et al. 1978
Cladoceran, *Daphnia pulex*	Zinc sulfate	45	48 hrs	LC50 (10 C)	1,200	Cairns, et al. 1978
Cladoceran, *Daphnia pulex*	Zinc sulfate	45	48 hrs	LC50 (15 C)	940	Cairns, et al. 1978
Cladoceran, *Daphnia pulex*	Zinc sulfate	45	48 hrs	LC50 (25 C)	280	Cairns, et al. 1978
Mayfly, *Ephemerella grandis*	Zinc sulfate	30-70	14 days	LC50	>9,200	Nehring, 1976

Table 6. (Continued)

Species	Chemical	Hardness (mg/l as $CaCO_3$)	Duration	Effect	Result* (µg/l)	Reference
Mayfly, *Ephemerella subvaria*	Zinc sulfate	54	10 days	LC50	16,000	Warnick & Bell, 1969
Stonefly, *Acroneuria lycorias*	Zinc sulfate	50	14 days	LC50	32,000	Warnick & Bell, 1969
Stonefly, *Pteronarcys californica*	Zinc sulfate	30-70	14 days	LC50	>13,900	Nehring, 1976
Midge, *Tanytarsus dissimilis*	Zinc chloride	47	10 days	LC50	37	Anderson, et al. 1980
Caddisfly, *Hydropsyche betteni*	Zinc sulfate	52	11 days	LC50	32,000	Warnick & Bell, 1969
Coho salmon, *Oncorhynchus kisutch*	Zinc sulfate	3-10	96 hrs	WBC-T counts depressed at 1/2 96-hr LC50	500	McLeay, 1975
Sockeye salmon, *Oncorhynchus nerka*	Zinc chloride	20-90	18 mos	None (embryo to smolt)	242	Chapman, 1978a
Sockeye salmon, *Oncorhynchus nerka*	Zinc chloride	53	115 hrs	LC50	447	Chapman, 1978a
Sockeye salmon, (Zn acclimated) *Oncorhynchus nerka*	Zinc chloride	53	115 hrs	LC50	>630	Chapman, 1978a
Sockeye salmon, (Zn acclimated) *Oncorhynchus nerka*	Zinc chloride	22	96 hrs	LC50	1,660	Chapman, 1978a
Cutthroat trout, *Salmo clarki*	Zinc chloride	34-47	14 days	LC50	670	Nehring & Goettl, 1974
Rainbow trout, *Salmo gairdneri*	Zinc sulfate	-	5 days	LC50	4,600	Ball, 1967
Rainbow trout, *Salmo gairdneri*	Zinc sulfate	240	48 hrs	LC50	4,000	Brown & Dalton, 1970

Table 6. (Continued)

Species	Chemical	Hardness (mg/l as $CaCO_3$)	Duration	Effect	Result* (µg/l)	Reference
Rainbow trout, *Salmo gairdneri*	Zinc sulfate	40	24 hrs	LC50 (5 C)	2,800	Cairns, et al. 1978
Rainbow trout, *Salmo gairdneri*	Zinc sulfate	40	24 hrs	LC50 (15 C)	1,560	Cairns, et al. 1978
Rainbow trout, *Salmo gairdneri*	Zinc sulfate	40	24 hrs	LC50 (30 C)	2,100	Cairns, et al. 1978
Rainbow trout, *Salmo gairdneri*	Zinc sulfate	14	21 days	LC50	500-1,000	Grande, 1967
Rainbow trout, *Salmo gairdneri*	Zinc sulfate	320	48 hrs	LC50	3,860	Herbert & Shurben, 1964
Rainbow trout, *Salmo gairdneri*	Zinc sulfate	320	48 hrs	LC50	2,460	Herbert & Van Dyke, 1964
Rainbow trout, *Salmo gairdneri*	Zinc sulfate	320	48 hrs	LC50	5,000	Herbert & Wakeford, 1964
Rainbow trout, *Salmo gairdneri*	Zinc acetate	-	96 hrs	LC50	550	Hale, 1977
Rainbow trout, *Salmo gairdneri*	Zinc sulfate	15-20	7 days	LC50	560	Lloyd, 1961
Rainbow trout, *Salmo gairdneri*	Zinc sulfate	320	3 days	LC50	3,500	Lloyd, 1961
Rainbow trout, *Salmo gairdneri*	-	38-54	14 days	LC50	410	Nehring & Goettl, 1974
Rainbow trout, *Salmo airdneri*	Zinc sulfate	25	5 days	LC50	135	Sinley, et al. 1974
Rainbow trout, *Salmo gairdneri*	Zinc sulfate	333	22 mos	LC10	1,055	Sinley, et al. 1974
Rainbow trout, *Salmo gairdneri*	Zinc sulfate	13-15	20 min	threshold avoidance level	5.6	Sprague, 1968

Table 6. (Continued)

Species	Chemical	Hardness (mg/l as $CaCO_3$)	Duration	Effect	Result* (µg/l)	Reference
Rainbow trout, Salmo gairdneri	Zinc sulfate	374	85 days	EC25 growth inhibition	1,120	Watson & McKeown, 1976
Brown trout, Salmo trutta	Zinc sulfate	14	21 days	LC50	500-1,000	Grande, 1967
Brown trout, Salmo trutta	-	22-35	14 days	LC50	640	Nehring & Goettl, 1974
Atlantic salmon, Salmo salar	Zinc sulfate	12-24	21 days	LC50	1,450	Farmer, et al. 1979
Atlantic salmon, Salmo salar	Zinc sulfate	12-24	21 days	LC50	1,600	Farmer, et al. 1979
Atlantic salmon, Salmo salar	Zinc sulfate	12-24	21 days	LC50	510	Farmer, et al. 1979
Atlantic salmon, Salmo salar	Zinc sulfate	12-24	21 days	LC50	1,460	Farmer, et al. 1979
Atlantic salmon, Salmo salar	Zinc sulfate	12-24	21 days	LC50	340	Farmer, et al. 1979
Atlantic salmon Salmo salar	Zinc sulfate	12-24	21 days	LC50	350	Farmer, et al. 1979
Atlantic salmon Salmo salar	-	14	21 days	LC50	100-500	Grande, 1967
Atlantic salmon, Salmo salar	-	14	96-182 hrs	Incipient lethal level	150-1,000	Zitko & Carson, 1977
Brook trout, Salvelinus fontinalis	-	12-24	14 days	LC50	960	Nehring & Geottl, 1974
Goldfish, Carassius auratus	Zinc sulfate	40	24 hrs	LC50 (5 C)	103,000	Cairns, et al. 1978
Goldfish, Carassius auratus	Zinc sulfate	40	24 hrs	LC50 (15 C)	40,000	Cairns, et al. 1978
Goldfish, Carassius auratus	Zinc sulfate	40	24 hrs	LC50 (30 C)	24,000	Cairns, et al. 1978

Table 6. (Continued)

Species	Chemical	Hardness (mg/l as $CaCO_3$)	Duration	Effect	Result* (µg/l)	Reference
Golden shiner, *Notemigonius crysoleucus*	Zinc sulfate	40	24 hrs	LC50 (5 C)	11,400	Cairns, et al. 1978
Golden shiner, *Notemigonius crysoleucus*	Zinc sulfate	40	24 hrs	LC50 (15 C)	7,760	Cairns, et al. 1978
Golden shiner, *Notemigonius crysoleucus*	Zinc sulfate	40	24 hrs	LC50 (30 C)	8,330	Cairns, et al. 1978
Fathead minnow, *Pimephales promelas*	Zinc sulfate	203	10 mos	EC65 fecundity	180	Brungs, 1969
Fathead minnow, *Pimephales promelas*	Zinc acetate	20	96 h	LC50	880	Pickering & Henderson, 1966
Guppy, *Poecilia reticulatus*	Zinc sulfate	80	90 days	EC60 growth	1,158	Crandall & Goodnight, 1962
Striped bass (embryo), *Morone saxatilis*	-	137	96 hrs	LC50 (5 C)	1,850	O'Rear, 1972
Bluegill, *Lepomis macrochirus*	Zinc sulfate	40	24 hrs	LC50 (5 C)	23,000	Cairns, et al. 1978
Bluegill, *Lepomis macrochirus*	Zinc sulfate	40	24 hrs	LC50 (15 C)	19,100	Cairns, et al. 1978
Bluegill, *Lepomis macrochirus*	Zinc sulfate	40	24 hrs	LC50 (30 C)	8,850	Cairns, et al. 1978
Bluegill, *Lepomis macrochirus*	Zinc chloride	45	96 hrs	LC50 periodic low DO	2,350	Cairns & Scheier, 1957a
Bluegill, *Lepomis macrochirus*	Zinc sulfate	370	20 days	LC50 (DO 1.7)	7,200	Pickering, 1968
Bluegill, *Lepomis macrochirus*	Zinc sulfate	370	20 days	LC50 (DO 1.9)	7,500	Pickering, 1968
Bluegill, *Lepomis macrochirus*	Zinc sulfate	370	20 days	LC50 (DO 3.2)	10,700	Pickering, 1968

Table 6. (Continued)

Species	Chemical	Hardness (mg/l as $CaCO_3$)	Duration	Effect	Result* (µg/l)	Reference
Bluegill, *Lepomis macrochirus*	Zinc sulfate	370	20 days	LC50 (DO 3.2)	10,500	Pickering, 1968
Bluegill, *Lepomis macrochirus*	Zinc sulfate	370	20 days	LC50 (DO 5.4)	12,000	Pickering, 1968
Bluegill, *Lepomis macrochirus*	Zinc sulfate	370	20 days	LC50 (DO 5.3)	10,700	Pickering, 1968
Bluegill, *Lepomis macrochirus*	Zinc sulfate	-	1-24 hrs	Increased cough response	3,000	Sparks, et al. 1972a
Bluegill, *Lepomis macrochirus*	Zinc sulfate	51	3 days	Lethal to fry	235	Sparks, et al. 1972b
Bluegill, *Lepomis macrochirus*	Zinc phosphate	46	96 hrs	No death	32,000	Cairns, et al. 1971
			SALTWATER SPECIES			
Marine isopod, *Idotea baltica*	Zinc sulfate	-	96 hrs	40% mortality (35 g/kg sal.)	10,000	Jones, 1975
Marine isopod, *Idotea baltica*	Zinc sulfate	-	78 hrs	60% mortality (28 g/kg sal.)	10,000	Jones, 1975
Marine isopod, *Idotea baltica*	Zinc sulfate	-	72 hrs	75% mortality (21 g/kg sal.)	10,000	Jones, 1975
Marine isopod, *Idotea baltica*	Zinc sulfate	-	48 hrs	100% mortality (14 g/kg sal.)	10,000	Jones, 1975
Marine isopod, *Jaera albifrons*	Zinc sulfate	-	72 hrs	10% mortality (35 g/kg sal.)	10,000	Jones, 1975
Marine isopod, *Jaera albifrons*	Zinc sulfate	-	67 hrs	30% mortlity (3 g/kg sal.)	10,000	Jones, 1975
Marine isopod, *Jaera albifrons*	Zinc sulfate	-	52 hrs	80% mortality (0.4 g/kg sal.)	10,000	Jones, 1975

Table 6. (Continued)

Species	Chemical	Hardness (mg/l as $CaCO_3$)	Duration	Effect	Result* (µg/l)	Reference
Hermit crab (adult), *Pagurus longicarpus*	Zinc chloride	-	168 hrs	LC50	200	Eisler & Hennekey, 1977
Crab (larvae), *Rhithropanopeus harrisi*	Zinc chloride	-	16 days	Delayed development	50	Benijts-Claus & Benijts, 1975
Mummichog (adult), *Fundulus heteroclitus*	Zinc chloride	-	96 hrs	LC28	60,000	Eisler & Gardner, 1973
Mummichog (adult), *Fundulus heteroclitus*	Zinc chloride	-	24 hrs	Histological damage	60,000	Eisler & Gardner, 1973
Mummichog (adult), *Fundulus heteroclitus*	Zinc chloride	-	168 hrs	LC0	10,000	Eisler & Hennekey, 1977
Mummichog (adult), *Fundulus heteroclitus*	Zinc chloride	-	168 hrs	LC50	52,000	Eisler & Hennekey, 1977
Mummichog (adult), *Fundulus heteroclitus*	Zinc chloride	-	168 hrs	LC100	120,000	Eisler & Hennekey, 1977
Mummichog (adult), *Fundulus heteroclitus*	Zinc chloride	-	14 days	Increase in liver ALA-D enzyme activity	10,000	Jackim, 1973
Mummichog (adult), *Fundulus heteroclitus*	Zinc chloride	-	48 hrs	LC100	157,000	Eisler, 1967
Mummichog (adult), *Fundulus heteroclitus*	Zinc chloride	-	192 hrs	LC0	43,000	Eisler, 1967
Mummichog (adult), *Fundulus heteroclitus*	Zinc chloride	-	192 hrs	LC50	66,000	Eisler, 1967
Atlantic salmon (smolt), *Salmo salar*	Zinc sulfate	-	48 hrs	50% survival (3 g/kg sal.)	6,000	Herbert & Wakeford, 1964
Atlantic salmon (smolt), *Salmo salar*	Zinc sulfate	-	48 hrs	50% survival (7 g/kg sal.)	15,000	Herbert & Wakeford, 1964
Atlantic salmon (smolt), *Salmo salar*	Zinc sulfate	-	48 hrs	50% survival (14 g/kg sal.)	35,000	Herbert & Wakeford, 1964

Table 6. (Continued)

Species	Chemical	Hardness (mg/l as $CaCO_3$)	Duration	Effect	Result* (µg/l)	Reference
Atlantic salmon (smolt), *Salmo salar*	Zinc sulfate	-	48 hrs	50% survival (26 g/kg sal.)	28,000	Herbert & Wakeford, 1964
Rainbow trout (yearling), *Salmo gairdneri*	Zinc sulfate	-	48 hrs	50% survival (3 g/kg sal.)	15,000	Herbert & Wakeford, 1964
Rainbow trout (yearling), *Salmo gairdneri*	Zinc sulfate	-	48 hrs	50% survival (7 g/kg sal.)	25,000	Herbert & Wakeford, 1964
Rainbow trout (yearling), *Salmo gairdneri*	Zinc sulfate	-	48 hrs	50% survival (14 g/kg sal.)	85,000	Herbert & Wakeford, 1964
Rainbow trout (yearling), *Salmo gairdneri*	Zinc sulfate	-	48 hrs	50% survival (26 g/kg sal.)	35,000	Herbert & Wakeford, 1964
Protozoan, *Cristigera* sp.	Zinc sulfate	-	4-5 hrs	Reduced growth	125	Gray, 1974
Protozoan, *Cristigera* sp.	Zinc sulfate	-	-	Growth reduction	125	Gray & Ventilla, 1973
Polychaete, *Ctenodrilus serratus*	Zinc sulfate	-	21 days	Reduced survival	10,000	Reish & Carr, 1978
Sandworm (adult), *Nereis virens*	Zinc sulfate	-	168 hrs	LC50	2,600	Eisler & Hennekey, 1977
Polychaete, *Ophryotrocha diadema*	Zinc sulfate	-	21 days	Reduced survival	1,750	Reish & Carr, 1978
Polychaete, *Ophryotrocha labronica*	Zinc sulfate	-	13 hrs	LC50	1,000	Brown & Ahsanullah, 1971
Hard-shell clam (larva), *Mercenaria mercenaria*	Zinc chloride	-	10 days	LC50	195	Calabrese, et al. 1977
Hard-shell clam (larva), *Mercenaria mercenaria*	Zinc chloride	-	12 days	LC95	341	Calabrese, et al. 1977
Soft-shell clam (adult), *Mya arenaria*	Zinc chloride	-	168 hrs	LC50 (20 C)	3,100	Eisler & Hennekey, 1977

Table 6. (Continued)

Species	Chemical	Hardness (mg/l as $CaCO_3$)	Duration	Effect	Result* (µg/l)	Reference
Soft-shell clam (adult), *Mya arenaria*	Zinc chloride	-	168 hrs	LC50 (22 C)	1,550	Eisler, 1977a
Mud snail (adult), *Nassarius obsoletus*	Zinc chloride	-	72 hrs	Decreased oxygen consumption	200	MacInnes & Thurberg, 1973
Mud snail (adult), *Nassarius obsoletus*	Zinc chloride	-	168 hrs	LC50	7,400	Eisler & Hennekey, 1977
Hard-shell clam (embryo), *Mercenaria mercenaria*	Zinc chloride	-	42-48 hrs	LC100	279	Calabrese & Nelson, 1974
Hard-shell clam (larva), *Mercenaria mercenaria*	Zinc chloride	-	12 days	LC5	50	Calabrese, et al. 1977
Oyster (larva), *Crassostrea gigas*	Zinc sulfate	-	5 days	Substrate attachment inhibition	125	Boyden, et al. 1975
Oyster (larva), *Crassostrea gigas*	Zinc sulfate	-	48 hrs	Reduced development	125	Brereton, et al. 1973
Oyster (larva), *Crassostrea gigas*	Zinc sulfate	-	6 days	Growth inhibition	125	Brereton, et al. 1973
Oyster (larva), *Crassostrea gigas*	Zinc chloride	-	48 hrs	Abnormal shell development	70	Nelson, 1972
Oyster (larva), *Crassostrea virginica*	Zinc chloride	-	48 hrs	LC0	75	Calabrese, et al. 1973
Oyster (larva), *Crassostrea virginica*	Zinc chloride	-	48 hrs	LC100	500	Calabrese, et al. 1973
Sea urchin (spermatozoa), *Arbacia puctulata*	Zinc chloride	-	4 mins	Decreased motility	1,635	Young & Nelson, 1974
Sea urchin (embryo), *Arbacia puctulata*	-	-	15 hrs	Abnormal development	1,250	Waterman, 1937
Starfish (adult), *Asterias forbesi*	Zinc chloride	-	168 hrs	LC50	2,300	Eisler & Hennekey, 1977

Table 6. (Continued)

Species	Chemical	Hardness (mg/l as $CaCO_3$)	Duration	Effect	Result* (µg/l)	Reference
Starfish (adult), *Asterias forbesi*	Zinc chloride	-	24 hrs	Equilibrium loss	2,700	Galtsoff & Loosanoff, 1939

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* Results are expressed as zinc, not as the compound.

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Mammalian Toxicology and Human Health Effects

INTRODUCTION

More than 100 years ago it was shown that zinc was essential for the growth of Aspergillus niger. It was then shown that it was an essential metal for plant life. In the 1930's, the essentiality of zinc for the growth of rats was shown. Zinc has for a long time been regarded as an essential element for human beings but not until the 1960's was it shown that zinc deficiency could cause a certain syndrome and that therapy with zinc salts could alleviate or even cure the symptoms of zinc deficiency. During the recent past some other disease states including congenital diseases have been related to zinc. Zinc therapy has attracted the interest of clinicians. The evergrowing interest in the metabolism of zinc and the relationship between zinc and certain diseases has, during the last decades, been reflected in a large number of reviews and books (Brewer and Prasad, 1977; Halsted, et al. 1974; National Research Council, 1978; Pories, et al. 1974; Prasad, 1966, 1976, 1978; Sandstead, 1973, 1975; Vallee, 1959; Underwood, 1977). The National Research Council (NRC) report contains 1,855 references and gives information not only on metabolism and essentiality of zinc for human beings but also much information on occurrence of zinc, analytical methods, and human health hazards from excessive exposure to zinc. Since this document relies to a large extent on the NRC report, reference will be given to chapters or page numbers in that report whenever it is quoted in this or following sections.

The information given will rely mainly on the previously mentioned references and specific references will only be given when there is information which might add to the understanding of the metabolism and health effects of zinc, especially in humans.

EXPOSURE

Ingestion from Water

The National Research Council (1978) (Chapter 2 pp. 25-28 and Chapter 11 pp. 269-271) summarized available data on zinc in drinking water and concluded that generally the concentrations were well below 5 mg/l. In a study by the U.S. Department of Health, Education and Welfare (U.S. DHEW, 1970) 2,595 water samples were tested and of them eight had zinc concentrations above the 5 mg/l level. The highest concentration found was 13 mg/l. The average zinc concentration was 0.19 mg/l. In water leaving treatment plants, Craun and McCabe (1975) found that all samples contained less than 5 mg/l of zinc, but that in cities with soft acidic water the concentrations increased in the distribution system. Tapwater could thus have concentrations around 5 mg/l. In a study by U.S. EPA (1975) it was found that in 591 water samples all had zinc concentrations below 4 mg/l.

Uncontaminated fresh water generally contains zinc at less than 0.01 mg/l (NRC, 1978). Analysis of filtered surface waters in the U.S. revealed that of 714 samples only 7 had concentrations exceeding 1 mg/l and that 607 (85 percent) had concentrations below 0.1 mg/l (Durum, et al. 1971).

The concentration of zinc in both natural waters and in drinking water is generally low, but may increase due to pollution of water systems or release of zinc from distribution systems and household plumbing, respectively.

Ingestion from Food

In the NRC document the content of zinc in different foodstuffs is listed in detail (Appendix A-I pp. 313-326). It was noted that meat products contain relatively high concentrations of zinc, whereas fruits and vegetables have relatively low concentrations and contribute little to the daily intake. Zinc concentrations in milk are generally low, but a high intake of milk can make an important contribution to daily intake of zinc.

Additional data are provided by Mahaffey, et al. (1975) who calculated that meats, fish, and poultry on an average contained 24.5 mg/kg of zinc, whereas grains (and cereal products) and potatoes only provided 8 and 6 mg/kg, respectively. These data were obtained from Food and Drug Administration (FDA) market basket studies which are based on the diets of males 15 to 20 years old. In the years 1973 and 1974 it was calculated that the daily intake in this age group was 18 and 18.6 mg/day of zinc, respectively. Greger (1977) calculated the daily intake of zinc in subjects living in an institution for the aged, with an average age of 75 years, and found that on an average the intake was 18.7 mg/day. In girls 12 to 14 years old, Greger, et al. (1978) found that the average intake of zinc was 10 mg/day.

In the "recommended dietary allowances" the National Research Council [National Academy of Sciences (NAS), 1974] recommended that adults should have a zinc intake of 15 mg/day, but pregnant women should have an intake of 20 mg/day and lactating women an intake of 25 mg/day. As a requirement of preadolescent children, 10 mg/day was recommended. In infants up to six months old, 3 mg/day was recommended and for children aged 0.5 to 1 year, 5 mg/day was suggested. Based on body weight the requirement for zinc would be about 0.5 mg/kg for the infant and about 0.2 mg/kg in the adult. These recommended doses take individual variations into account. An intake less than the recommended intake does not necessarily mean that zinc deficiency will occur.

A bioconcentration factor (BCF) relates the concentration of a chemical in aquatic animals to the concentration in the water in which they live. An appropriate BCF can be used with data concerning food intake to calculate the amount of zinc which might be ingested from the consumption of fish and shellfish. Residue data for a variety of inorganic compounds indicate that bioconcentration factors for the edible portion of most aquatic animals are similar, except that for some compounds bivalve molluscs (clams, oysters, scallops, and mussels) should be considered a separate group. An analysis (U.S. EPA, 1980) of data from a food survey was used to estimate that the per capita consumption of freshwater and estuarine fish and shellfish is 6.5 g/day (Stephan, 1980). The per capita consumption of bivalve molluscs is 0.8 g/day and that of all other freshwater and estuarine fish and shellfish is 5.7 g/day.

Bioconcentration factors are available for the edible portions of several aquatic species (Table 1).

TABLE 1

Bioconcentration Factors of Edible Portions of Aquatic Organisms

Species	BCF	Reference
Oyster (adult), *Crassostrea virginica*	16,700	Shuster and Pringle, 1969
Soft-shell clam, *Mya arenaria*	85	Pringle, et al. 1968
Soft-shell clam, *Mya arenaria*	43	Eisler, 1977
Mussel, *Mytilus edulis*	225	Phillips, 1977
Mussel, *Mytilus edulis*	500	Pentreath, 1973
Mussel, *Mytilus edulis*	282	Phillips, 1976
Crab, *Carcinus maenas*	8,800	Bryan, 1966

The geometric mean of the values for bivalve molluscs is 353, but the value for the crab seems too high, considering that values for the whole body of two species of fish were 51 (Farmer, et al. 1979) and 432 (Spehar, et al. 1978). Based on the available data for copper and cadmium, the mean BCF value for other species is probably about 1 percent of that for bivalve molluscs. If the values of 353 and 3.5 are used with the consumption data, the weighted average bioconcentration factor for zinc and the edible portion of all freshwater and estuarine aquatic organisms consumed by Americans is calculated to be 47.

Air quality data compiled in the NRC document (1978) show that zinc concentrations throughout the U.S. generally are less than 1 μg/m^3 (Chapter 3 p. 42-43). In 1975 and 1976, U.S. EPA (1979) observed zinc concentrations at approximately 50 National Air Surveillance Network sites throughout the U.S. Zinc concentrations is most areas were below 1 μg/m^3, quarterly average.

The air levels of zinc are, in most areas, fairly constant. As an example, Lioy, et al. (1978) presented data on zinc concentrations in New York City during the years 1972 to 1975 where the annual averages varied from 0.29 to 0.38 μg/m^3. Much higher concentrations have been reported near smelters. About 1.5 miles from a smelter in Kellogg, Idaho, Ragaini, et al. (1977) found in ambient air a yearly mean zinc concentration of 5 μg/m^3. The 24-hour values ranged from 0.27 to 15.7 μg/m^3. It should be mentioned that the average lead and cadmium concentrations were 11 and 0.8 μg/m^3, respectively, indicating very severe environmental pollution. The U.S. data may be compared to data from 15 cities in a heavily industrialized European country, Belgium (Kretzschmar, et al. 1977). During the period May 1972 to April 1975 the average concentrations in 15 locations were from 0.22 to 3.05 µg/m^3. The highest value recorded during 24 hours was 57 µg/m^3.

These data from industrialized countries may be compared to background levels of zinc which have been measured at the South Pole and over the Atlantic Ocean. At the South Pole an average concentration of 0.03 ng/m^3 was found. In the air over the Atlantic Ocean concentrations were from 0.3 to 27 ng/m^3 (Duce, et al. 1975; Maenhaut and Zoller, 1977; Zoller, et al. 1974).

In cigarettes and other tobacco products zinc concentrations have been reported to vary from 12.5 to 70 µg/g (Menden, et al. 1972; Dermelj, et al. 1978; Franzke, et al. 1977). In the studies by Menden, et al. and Franzke, et al., the amount of zinc in the mainstream smoke was determined by simulated smoking in a smoking machine. Menden, et al. found in two brands of cigarettes that 0.06 and 0.36 µg, respectively, was in the mainstream leaving the cigarette, whereas Franzke, et al. found in 16 brands that from 0.12 to 0.92 µg was in the same fraction. These data indicate that by smoking 20 cigarettes up to 20 µg of zinc might be inhaled. There might have been some differences in experimental techniques, since Menden, et al. found that about 85 percent of the zinc remained in the ash, whereas Franzke, et al. found that in some cigarettes only about 10 percent remained in the ash.

The major source of zinc for the general population in the U.S. is food. The average intake is generally above 10 mg in adults. An individual inhaling air with an average concentration of 5 µg/m^3, would have an additional daily intake of 100 µg, assuming that he inhales 20 m^3 of air per day. Smoking would contribute even less than that. Compared to the intake via food, airborne exposure is insignificant.

The intake via drinking water might be of more significance. Levels around 1 mg/l are not uncommon and levels around 5 mg/l have been reported. Assuming a daily intake of 2 liters of water this might result in daily intakes of 2 and 10 mg, respectively. The latter amount might double the intake for people on a low dietary intake, but the total intake will still be within recommended limits. In people with recommended daily intakes of zinc, i.e., 15 to 20 mg, the additional intake via water will result in total daily intakes of 25 to 30 mg. As discussed later, the homeostatic regulation of zinc ensures that such amounts and even larger amounts can generally be well tolerated.

PHARMACOKINETICS

Absorption

The fate of inhaled particles containing zinc will depend on particle size and solubility as well as functional state of the lungs. The quantitative features of the deposition patterns of particles have been reviewed by the Task Group on Lung Dynamics (1966) and the Task Group on Metal Accumulation (1973). There are no quantitative data on the deposition and absorption of zinc compounds, but experiments on human beings by Sturgis, et al. (1927) and Drinker, et al. (1927) indicated that both zinc oxide fumes and zinc oxide powder with very small particle size were deposited in the alveoli. That inhaled zinc is absorbed is shown by the finding of increased serum and plasma levels of zinc in exposed workers. It should be pointed out, however, that part of the inhaled material will be transported to the gastrointestinal tract via ciliary activity and some zinc may also be absorbed that way.

The absorption of ingested zinc will depend mainly on the zinc status of the organism. The presence or absence of other nutritional constituents may also influence absorption.

Spencer, et al. (1965) showed in human beings that ^{65}Zn as the chloride was rapidly taken up, with plasma peak values within four hours. It was calculated that about 50 percent was absorbed, but with a wide range (20 to 80 percent). In that study it was not possible to show that the amount of calcium in the diet influences the uptake of zinc from the gut. There are difficulties in assessing the absorption of zinc, since there is also considerable excretion of absorbed zinc via the gastrointestinal tract. There are also several other earlier studies which show that there are wide variations in the absorption rates of ingested zinc (NRC Chapter 6 pp. 145-154).

The protein content of the diet has been shown to influence the uptake of zinc. In studies done on people with zinc deficiency it has been noted that the effect of zinc therapy is enhanced by a simultaneous administration of protein. It has also been shown that the absorption of zinc will be reduced if the diet contains large amounts of phytate especially in the presence of large amounts of calcium (NRC Chapter 7 pp. 183-187). Since phytates are found in cereals, zinc in vegetable diets that include large amounts of unleavened bread may be less available for absorption. Arvidsson, et al. (1978) found that the average absorption of ^{65}Zn added to bread during baking was 25 percent ranging from 12.2 to 39.1 percent in 11 subjects. The study was repeated after one month and the same average absorption was found. In this study, the influence of phytate seems to have been small. The fiber content of the diet may influence the uptake of zinc (Sandstead, et al. 1978). Zinc in animal proteins seems to be easily available and thus meat is a good source of zinc.

The influence of oral contraceptive agents on the absorption of zinc was studied in 14 women. They were compared with eight women who did not take contraceptive pills (King, et al. 1978). All were of similar age. Zinc was administered as a stable isotope, ^{70}Zn, and the absorption was determined from the difference between intake and fecal output of the stable isotope which was measured by neutron activation analysis. Among the women taking the contraceptive agents, the average absorption was 33 percent and in the control group it was 46 percent. The difference, however, was not statistically significant, and the authors concluded that there was no difference in absorption.

The mechanisms for absorption of zinc are homeostatically controlled, and data from animal experiments suggest that several proteins and low molecular weight compounds may be involved in the absorption process. There is evidence that metallothionein, a low molecular weight, metal-binding protein, in the intestinal mucosa may bind zinc (Richards and Cousins, 1977). Zinc binding ligands with molecular weights lower than metallothionein have been found in animals. Evans, et al. (1975) proposed that such a compound was produced in the pancreas and through the pancreatic secretions could bind zinc in the gastrointestinal tract and enhance absorption.

Of special interest is a zinc binding ligand which occurs in human milk, but has not been found in bovine milk. In 1976, Eckhert, et al. (1977) reported that gel chromatography of cow's milk and human milk showed that in cow's milk zinc was associated with high molecular weight fractions, whereas in human milk it was mainly associated with low molecular weight fractions. This species difference was taken by these authors as an explanation for the congenital disease acrodermatitis enteropathica which usually occurred when infants were weaned from human breast milk. Similar results were reported by Evans and Johnson (1976) who thought that the low molecular weight zinc binding ligand in milk was similar to the ligand found in pancreatic secretions from the rat. During the last years several studies have been performed to isolate and identify this ligand (Song and Adham, 1977; Evans and Johnson, 1977; Schricker and Forbes, 1978; Lonnerdal, et al. 1979; Evans and Johnson, 1979). The data are controversial and at present no certain conclusions can be drawn regarding the nature of the ligand or ligands. It has also been shown by Cousins, et al. (1978) that degradation products of intestinal proteins including metallothionein may occur as low molecular weight zinc binding complexes in rat intestine. The role of ligands in zinc absorption has recently been discussed by Cousins (1979).

Keen and Hurley (1977) have shown that zinc salts will be absorbed through intact skin of the rat. According to these authors the amount of zinc absorbed was higher in zinc-deficient animals and was of a magnitude which might be clinically significant.

Hallmans (1978a,b) showed that in rats with excisional wounds there was a high absorption of zinc from gauzes containing zinc sulfate. At a concentration of 20 percent there were even systemic effects. Hallmans concluded that the absorption from zinc sulfate was higher than from zinc oxide. Hallmans (1977) also showed that in humans treated for burns with gauzes containing zinc oxide, there was absorption of zinc.

Anteby, et al. (1978) reported that in women using an intrauterine device containing copper and zinc, a slight rise in serum zinc could be shown, but no abnormal values were found.

Distribution

Zinc is found in erythrocytes mainly due to the presence of the zinc metalloenzyme carbonic anhydrase and in leucocytes where several zinc metalloenzymes are present. In plasma, zinc is mainly bound to albumin and it is thought that the binding is to one of the histidine moieties of the albumin molecule. About one-third of the serum zinc is bound to an α_2-macroglobulin and a few percent to amino acids. In the albumin and the amino acids there is an exchange of zinc, whereas there is no exchange with zinc in the α_2-macroglobulin. The zinc bound to amino acids constitutes the diffusible serum zinc (Giroux, 1975; Giroux, et al. 1976; NRC, 1978).

Of special interest is the relationship between zinc and histidine. It has been shown in human beings that oral administration of histidine will cause decreases in serum zinc and an increase in urinary zinc excretion (Henkin, et al. 1975). This observation has also been made in experiments on rats (Freeman and Taylor, 1977) and dogs (Yunice, et al. 1978). The latter authors also showed that cysteine caused a considerable increase in excretion of zinc. This is thought to be one explanation for the losses of zinc seen in patients given parenteral hyperalimentation, since the fluids given usually contained large amounts of essential amino acids, without sufficient amounts of essential metals (Agarwal and Henkin, 1978; Kumar, 1976).

In the tissues, the highest concentrations of zinc are found in the male reproductive system where the prostate has the highest content. High concentrations of zinc also occur in the muscle, bone, liver, kidney, pancreas, and some endocrine glands, especially the thyroid. The largest amounts of zinc are found in the muscles and the bone. Within tissues there may be variation; in the human prostate gland the highest zinc concentrations are found in the lateral prostate and the lowest in the interior and inner prostate. Also significant is the finding that semen has a high zinc content. In most organs there are relatively small variations in zinc levels during a lifetime except that in the newborn, zinc concentrations generally are higher than later in life. It should also be pointed out that the zinc content of the kidney and liver will, to a large degree, depend on the cadmium concentrations, and renal zinc concentrations will vary with age (Elinder, et al. 1978; Piscator and Lind, 1972; Schroeder, et al. 1967). Regarding the form in which zinc is stored in different organs, zinc is generally an essential component of many enzymes. Zinc is also found in metallothionein.

Excretion

Zinc is mainly excreted via the gastrointestinal tract but part of that zinc is reabsorbed. Urinary excretion of zinc is relatively small but with certain conditions, i.e., extreme heat or exercise, much larger quantities may be excreted in sweat (Cohn and Emmett, 1978; Hohnadel, et al. 1973). Zinc is also excreted via hair and milk, and in the female there is a placental transfer to the fetus.

Losses of zinc may also occur via the skin and menstrual blood losses. Molin and Wester (1976) determined by neutron activation the zinc content of epidermis. They calculated that the daily losses by desquamation would be about 20 to 40 µg, only about one-tenth (1/10) of the urinary excretion.

The long-term biological half-time of zinc will depend on the zinc status; it has been shown that after oral intake or injection of ^{65}Zn to human beings, the half-time may vary from about 200 to about 400 days, depending on the zinc status (NRC Chapter 6 pp. 151-154). Arvidsson, et al. (1978) gave eight subjects single injections of ^{65}Zn. After the injection, measurements were taken for 84 to 190 days. The slow component for the half-time of the injected zinc for this group was on an average 247 days. Kennedy, et al. (1978) found that the average half-time was 412 days in 19 female patients undergoing treatment for rheumatoid and osteoarthritis. They were given an oral dose of ^{65}Zn. In certain body compartments, e.g., bone, the half-time may be considerably longer (NRC Chapter 6 pp. 149-154).

Metallothionein was briefly discussed in previous reports and books concerning zinc, but during the last several years there has been an enormous increase in the number of papers on this protein. Recently a very comprehensive report on metallothionein has been prepared (Nordberg and Kojima, 1979). Mammalian metallothionein is a protein with a molecular weight of 6,000 to 7,000 which is characterized by a very special amino acid composition, a high cysteine content, but lack of aromatic amino acids and histidine. Metallothionein was first discovered in equine renal cortex by Margoshes and Vallee (1957) and has now been shown to occur in most mammalian tissues, and also in lower organisms. Total metal content of metallothionein can reach 6 to 7 g atoms per mole. The metals generally found in metallothionein are zinc, copper, and cadmium. The relative occurrence of these metals will depend on a number of factors. In fetal liver metallothionein, zinc and copper are the major constituents, whereas in animals exposed to cadmium, cadmium will be the dominating metal especially in the renal protein. A number of factors can induce the synthesis of metallothionein. In addition to administration of the above-mentioned metals, metallothionein synthesis seems also to be indirectly induced by factors that might influence zinc metabolism. Thus, environmental stresses of different kinds may induce the synthesis.

With regard to zinc metabolism, it has been shown that parenteral or dietary administration of zinc will cause an increase of the synthesis of metallothionein (Bremner and Davies, 1975; Richards and Cousins, 1975a,b, 1977). Recently, it was shown that hepatic zinc was increased and metallothionein synthesis stimulated in response to several environmental stresses, such as cool and hot environments, burns, and exercise (Oh, et al. 1978). Food restriction and bacterial infections have been shown to cause such changes (Bremner and Davies, 1975; Richards and Cousins, 1976; Sobocinski, et al. 1978). Failla and Cousins (1978) demonstrated that glucocorticoids *in vitro* stimulated the uptake of zinc in liver parenchymal cells, a process that required synthesis of metallothionein. Such findings indicate that metallothionein may serve as a regulator of plasma zinc levels and constitute an easily available pool for acute replacements of zinc in certain situations. Similar indications are given by reports from several investigators of finding large amounts of metallothionein containing zinc and copper in fetal livers (Bremner, et al. 1977; Hartman and Weser, 1977; Ryden and Deutsch, 1978). Much is still unknown about the biological function of metallothionein, but there is no doubt that this protein must play a very important role in the regulation of zinc in the mammalian body (Nordberg and Kojima, 1979).

In the National Research Council report (1978), extensive information is given on concentrations of zinc in blood, urine and tissues (Chapter 6 pp. 123-145). The NRC report concluded that the mean serum-zinc concentration in humans is approximately 1 mg/l, the same in healthy men and women. The zinc content of whole blood will be about five times higher than the serum level, since the concentration in the red cells is about 10 times the amount found in serum. A lowering of the serum concentrations of zinc may be seen in women taking contraceptive pills, during pregnancy, and as a result of certain stresses such as infections. In the same individual the zinc concentration in serum will be higher than in plasma mainly due to the release of zinc from platelets (Foley, et al. 1968). In 14 subjects the mean serum level was 1.15 mg/l and the mean plasma level 0.98 mg/l, the average difference being 16 percent.

The influence of age and sex on plasma zinc levels was studied by Chooi, et al. (1976). They found that in both males and females there was a decrease in plasma zinc from age 20 to age 90. Between men and women below the age of 50 no difference in plasma zinc levels could be noted between the sexes. However, females using contraceptive agents had lower zinc levels than women who did not take contraceptive agents. Average plasma levels in the groups studied were around 0.7 mg/l.

In a recent report, Hartoma (1977) stated that men had higher serum zinc levels than women. The average concentration in 154 male blood donors was 1.24 mg/l (range 0.74 to 2.2 mgl), and in 95 women it was 1.11 mg/l (range 0.64 to 1.82 mg/l). The difference was highly significant according to the author. It was not stated to what extent the women took contraceptive pills. Hartoma also found that there was a slight tendency to a lowering of the serum concentration of zinc in men with increasing age, and that there was a significant correlation between serum zinc and serum testosterone in males aged 36 to 60 years. In men 28 to 35 years of age, there was a negative correlation, which was not significant. In these two studies plasma and serum levels, respectively, were lower and higher than earlier reported data which indicates that methodological problems in sampling and analysis may still exist. In both studies samples were taken in the morning after overnight fasting.

In the NRC report (Chapter 6 p. 129) it was stated that approximately 0.5 mg of zinc is excreted in the urine every 24 hours by healthy persons. Additional data have been provided by Elinder, et al. (1978) who studied the urinary excretion of zinc in different age groups. They found that there was a tendency towards a higher zinc excretion in smokers than in nonsmokers. Among nonsmokers there was a tendency to decreased zinc excretion from about age 20 to higher ages (Table 2).

The tissue concentrations of zinc are generally higher in the newborn. After the first year of life there are fairly small changes in the zinc levels in most organs except the kidney where the zinc concentrations are dependent on the accumulation of cadmium (Elinder, et al. 1977; Piscator and Lind, 1972; Prasad, 1976). In the liver the zinc level is constant during a lifetime. In the pancreas there is a decrease in zinc levels with increasing age on a wet weight basis, whereas if the pancreas values are calculated on an ash weight basis that decrease is not seen (Elinder, et al. 1977). This is in agreement with Schroeder, et al. (1967). In the study by Elinder, the average concentrations of zinc in liver and pancreas were 45 (s.d. = 13.6) and 27 (s.d. = 7.2) mg/kg wet weight, respectively. In these organs the concentrations of

TABLE 2

Zinc Concentrations in the Urine of Swedish People†

Group	Number of Persons	Zinc, Average (a)* (mg/g of creatinine)	Standard Deviation (a)*	Zinc, Calculated Average (mg/24 hr)
Men, non-smokers (age in years)				
2 to 9	4	0.86	0.23	0.33
17 to 19	10	0.38	0.19	0.71
20 to 29	10	0.32	0.13	0.59
30 to 39	10	0.29	0.10	0.49
40 to 49	16	0.25	0.16	0.39
50 to 59	15	0.32	0.09	0.45
60 to 69	9	0.27	0.17	0.35
70 to 79	11	0.40	0.18	0.46
80 to 89	9	0.35	0.12	0.35
Men, smokers (age in years)				
40 to 49	5	0.35	0.19	0.55
50 to 59	5	0.39	0.09	0.55
66	1	0.32	--	0.41
75	1	0.27	--	0.31
Women, non-smokers (age in years)				
3	4	1.23	0.21	0.37
40 to 49	10	0.23	0.17	0.20
50 to 59	10	0.47	0.38	0.34

†Source: Elinder, et al. 1978.

*a, arithmetic averages.

zinc were normally distributed, whereas zinc concentrations in renal cortex had a log-normal distribution. When the renal zinc bound to metallothionein (assuming a cadmium-zinc ratio of 1.0 in metallothionein) was subtracted from total zinc, the basal zinc concentrations thus obtained had a normal distribution (Elinder, et al. 1977). The highest concentrations of zinc are found in the prostata, where the concentration is about 100 mg/kg wet weight. In human semen concentrations of 100 to 350 mg/l have been reported. The zinc concentrations in hair will vary depending on age and geographical location (MRC Chapter 6 pp. 140-141). Sorenson, et al. (1973) found that in 13 communities in the U.S. the average zinc concentration in hair from adults varied from 148 to 210 mg/kg. The newborn has zinc levels in hair similar to levels in the adult, but at age 1 to 4 the levels are lower than in adults (Hambidge, et al. 1972; Petering, et al. 1971). Zinc concentrations in hair will decrease during pregnancy (Baumslag, et al. 1974; Hambidge and Droegemueller, 1974). The determination of zinc in hair has been used as a screening tool for zinc deficiency (Hambidge, et al. 1972). The total body store of zinc in adult humans has been estimated to be 2.3 mg for a 70 kg man (NRC Chapter 6 p. 123).

The homeostatic regulation of zinc absorption in the rat was studied by Evans, et al. (1973). Rats fed an optimal intake of zinc were compared to rats which had been on a diet for 7 and 13 days, respectively, containing less than 1 mg/kg of zinc. Whereas, in the controls the absorption was about 15 percent, measured by examining the radioactivity in the carcass one hour after a gastric dose of ^{65}Zn, it was about 35 and 50 percent, respectively, in the two experimental groups.

Weigland and Kirchgessner (1978) studied the homeostatic mechanisms for zinc absorption in 36 weanling rats, where in groups of six they were given a diet with the following zinc contents: 5.6, 10.6, 18.2, 38, 70, and 141 mg/kg. After six days the animals had adjusted to the respective intakes and the absorption of zinc was from 100 to 34 percent in inverse relation to the intake of zinc. The true zinc absorption and the fecal excretion of endogenous zinc could be determined by measuring the turnover of radioactive zinc which had been injected at the start of the experiment. The figure of 100 percent seems surprisingly high, but these were weanling rats which were growing rapidly. This may also explain the relatively high absorption figure for the group receiving 141 mg/kg feed of zinc. The daily zinc retention was the same in the groups receiving 38, 70, and 141 mg/kg, whereas it was lower in the groups receiving 5.6, 10.6, and 18.2, indicating that in this study this supply was not sufficient. In the three highest exposure groups both total absorption and total fecal excretion of endogenous zinc increased in proportion to the daily intake.

The homeostatic regulation of ingested zinc was also studied by Ansari, et al. (1975). Male rats were given a diet containing 53 ppm zinc, and at different times groups were given a diet with 600 mg/kg of added zinc beginning 7, 14, 21, or 42 days before sacrifice. One week before sacrifice each rat was given, by gavage, an oral dose of ^{65}Zn as the chloride. Feces were collected for seven days. The elimination of fecal zinc was similar in all groups except the control group irrespective of length of exposure, whereas the fecal elimination of ^{65}Zn increased with length of exposure. Also analysis of tissues revealed that the longer the exposure to the high zinc level in the diet the more rapidly ^{65}Zn was eliminated. Tissue levels of stable zinc were only slightly influenced by the high zinc content of the diet. Only in the liver could a significant increase in the zinc level be noted. Levels in the kidneys, muscle tissue, and the heart did not differ from controls. These results also show the extreme capacity of the organism to handle excess zinc in the diet. They also show how rapid the exchange will be between absorbed zinc and tissue stores of zinc.

Ansari, et al. (1976) gave male rats dietary zinc at levels of from 1,200 to 8,400 ppm zinc for three weeks. One week before sacrifice each rat was given ^{65}Zn as the chloride by gavage and after that feces were collected for one week. The high zinc content of the diet did not affect weight gains, feed consumption, or produce any obvious signs of toxicity. In controls 65 percent of the ^{65}Zn was eliminated in one week in contrast to 86 percent in the rats given 1,200 ppm zinc in the diet. At still higher levels of dietary zinc there was no further increase of fecal ^{65}Zn. Rats given 1,200 ppm zinc in the diet had significantly higher levels of stable zinc in the liver, kidney, and tibia than controls, whereas there was no change in concentrations in the heart and muscle tissue. No further increase was seen at levels of 2,400 to 7,200 ppm in the diet, but at 8,400 ppm level a new increase was seen, also in the heart but not in muscle tissue.

The amount of radioactive zinc was, at all exposure levels, only a few percent of the amount found in the controls. There were no obvious changes with increasing dietary zinc, except in the tibia where, at the highest levels, there occurred an increase compared to the previous levels. In the heart and muscle tissue there was a slight but continuous decrease. In the liver and kidneys there was no change. The authors concluded that the data indicated that there was a good homeostatic control in the range 2,400 to 7,200 ppm. The authors also concluded that the homeostatic regulation of zinc was much more effective in the rat than in calves. Stake, et al. (1975) found that calves given a diet containing 600 mg/kg of zinc after one week had considerably higher zinc levels in the liver, kidneys, and pancreas than calves fed a diet containing 34 mg/kg. There was, however, no change in heart or muscle zinc levels.

The topics of zinc essentiality and zinc deficiency have been extensively treated in the National Research Council report (1978) and also in a recent review by Prasad (1978). In 1934, it was shown by Todd, et al. (1934) that zinc was necessary for the growth of rats and since then many studies have been made on the essentiality of zinc, including studies of humans.

In humans, zinc is necessary for normal growth and for normal development of the gonads. Prasad, et al. (1963) found that in certain villages in Egypt many subjects exhibited a syndrome characterized by dwarfism and anemia, hypogonadism, hepatosplenomegaly, rough and dry skin, and mental lethargy. There, young persons had a very low intake of animal proteins with bread as their main food. Zinc deficiency was demonstrated by the finding that zinc concentrations in plasma, red cells, and hair were decreased; that subjects had a higher turnover of radioactive zinc than normal; and that the excretion of zinc in feces and urine was less than in controls. Improvements were seen after oral administration of zinc, with a still greater effect observed upon additional protein supplementation.

Similar syndromes have been reported in other parts of the world. There are, however, studies that show that zinc deficiency with less pronounced symptoms may be more common than thought earlier. In the U.S., evidence of symptomatic zinc deficiency has been found in Colorado by Hambidge, et al. (1972). Zinc concentrations in hair were used as an index of the zinc status. Hambidge, et al. found that in 132 children ages 4 to 16, 10 children had hair zinc concentrations below 70 mg/kg, whereas most children had concentrations above 125 mg/kg. Eight out of ten of these children were found to have heights at the lower range for their age group. Poor appetite and a low intake of meat was thought to be one reason for the zinc deficiency. In these children hypogeusia (impaired taste acuity) was also found. After zinc supplementation, 1-2 mg zinc sulfate/kg body weight/day for 1-3 months, this condition was normalized. An increase in hair zinc could be shown parallelling the supplementation with zinc. In five children with hair zinc levels of 10 to 63 mg/kg before therapy, the levels were 67 to 170 mg/kg after four months of therapy. There are studies in other parts of the U.S. showing that low zinc levels in children's hair are not an uncommon finding (Prasad, 1978).

The reason for the signs and symptoms caused by the zinc deficiency is not clear, but it is known from a number of studies in a variety of organisms including human beings (NRC Chapter 8) that zinc is an essential constituent of many metalloenzymes. Typical examples of such metalloenzymes are alcohol dehydrogenase, carboxypeptidase, leucine aminopeptidase, alkaline phosphatase, carbonic anhydrase, RNA-polymerase, and DNA-polymerase. Also, thymidinekinase is thought to be a zinc dependent enzyme. Zinc may be involved in the synthesis and catabolism of RNA and DNA.

In addition to nutritional zinc deficiency, which is caused solely by a low dietary zinc intake, there are instances of zinc deficiency which are thought to have other causes. These are:

(1) Zinc deficiency in dialysis patients, which has been attributed to depletion of body zinc stores (Atkin-Thor, et al. 1978);

(2) Zinc deficiency after intravenous hyperalimentation, which might lead to increased excretion of zinc because of the large amounts of amino acids in the infusion fluids (Bernstein and Leyden, 1978; Freeman, et al. 1975);

(3) Zinc deficiency after excessive alcohol ingestion (Ecker and Schroeter, 1978; Weismann, et al. 1978); and

(4) Zinc deficiency after operations such as intestinal bypass surgery (Atkinson, et al. 1978; Weismann, et al. 1978) The signs noted are generally changes in the skin and hypogeusia.

There is also a rare congenital disease called acrodermatitis enteropathica which generally occurs in children after weaning. As has been discussed earlier, human milk seems to contain a factor or factors necessary for the absorption of zinc. Signs in this disease may come from many organs, among them the skin, central nervous system, and the gastrointestinal tract. As in other zinc deficiencies in children, there will be retarded growth and hypogonadism. Large oral doses of zinc will correct the condition.

Prasad, et al. (1978b) have recently reported on experimental zinc deficiency in humans. They studied four male volunteers who were hospital patients with various diseases. They were given a diet containing Zn at a level of about 3 mg/day for several weeks. In order to decrease the zinc intake it was necessary to give subjects cereal protein instead of animal protein during the study. In all subjects considerable weight losses occurred during the zinc depletion period. The plasma zinc level decreased significantly in all subjects and in 3 of 4 subjects there was a decrease in zinc excretion. Connective tissue was analyzed in two patients; during the period of low zinc intake thymidinekinase activity could not be detected, whereas after zinc supplementation it became close to the normal values. Also, plasma alkaline phosphatase activity decreased along with a decrease in plasma lactic dehydrogenase activity during the zinc depletion. In the connective tissue the RNA and DNA ratio showed changes during the restriction period.

EFFECTS

Zinc deficiency will not be covered in this section since it has been discussed in a previous section; the emphasis will be on the effects caused by excessive exposure to zinc via inhalation or via ingestion. The literature on such adverse health effects is limited. One probable reason for the limited information is that zinc has generally been accepted as a beneficial substance and adverse effects have neither been expected nor looked for.

Effects on the lungs and systemic effects after inhalation of zinc compounds have only been reported from occupational settings. A special case is the lung damage seen after inhalation of zinc chloride from smoke bombs. As will be discussed later, not only zinc chloride but also the hydrochloric acid formed are of importance for the development of such effects. Health effects observed in workers exposed to zinc and the results of some studies on animals will be discussed. Information on the health hazards of zinc will also be found in most textbooks on occupational hygiene and in the recent National Institute on Occupational Safety and Health (NIOSH) criteria document on zinc oxide (NIOSH, 1975).

Acute, Subacute, and Chronic Toxicity

Most of our knowledge about metal fume fever and its relationship to exposure to zinc oxide fumes comes from the beginning of the century when there was extensive research on this acute type of poisoning (Drinker, et al. 1927, 1928; Sturgis, et al. 1927). Reviews on metal fume fever, often also containing case reports, have been published in large numbers (Anseline, 1972; Hegsted, et al. 1945; Kehoe, 1948; Rohrs, 1957). Metal fume fever is described in all textbooks on occupational hygiene. In summarys it should also be mentioned that metal fume fever has not only been associated with inhalation of zinc oxide fumes, but with many other metal fumes which may produce similar symptoms.

Metal fume fever only appears after exposure to freshly produced metal fumes (McCord, 1960; Rohrs, 1957) which can penetrate deep into the alveoli. Zinc oxide dust or other metal dusts are not capable of producing the disorder. Typical for metal fume fever is symptom occurrence within a few hours after exposure. The symptoms may persist for 1 to 2 days and are characterized by influenza-like symptoms such as headache, fever, hyperpnea, sweating, and muscle pains. Among the laboratory findings leukocytosis is the most prominent. There have never been any fatalities from metal fume fever, nor does it cause long-term sequelae. Metal fume fever generally occurs at the beginning of the working week when the worker has not been exposed for a couple of days, and further exposure will not cause new symptoms. This disease has also been given the name "Monday fever." It has been suggested by McCord (1960) that there is an allergic basis for the mechanism of metal fume fever. Several theories have been put forward, but there is no definite evidence for any of the proposed different mechanisms for this reaction. One reasonable theory is that the metal fume penetrates deep into the alveoli, and combines with proteins which might act as sensitizing agents. There is a lack of data on the levels of zinc oxide fumes in air that might cause the disease. In a study by Sturgis, et al. (1927) two subjects were exposed to zinc oxide fumes at a level of 600 mg zinc/m^3. It was calculated that the subjects inhaled 48 and 74 mg zinc, respectively.

There was a report on acute emphysema in cattle reported to have been exposed to zinc oxide fumes (Hilderman and Taylor, 1974). This episode occurred in a barn where oxyacetylene cutting and arc welding of galvanized pipe were done during remodeling of the barn. Three heifers were severely affected and within a short time all three died. Autopsy showed severe changes in the lungs with edema, emphysema, and hemorrhages. Zinc concentrations in liver, kidney, and lungs were not above normal values in two animals examined. In this case, a galvanized material was suspected but the extremely severe condition caused by the fumes showed either that cattle are extremely sensitive to zinc oxide fumes or that other metals (such as cadmium) might have been responsible.

Acute pulmonary damage and even death may occur after the inhalation of zinc chloride which is the major component in smoke coming from so-called "smoke bombs" which are often used in military exercises. Accidental inhalation of such smoke in confined spaces may rapidly lead to severe disease, but it should be pointed out that the toxic action may not only be due to the zinc. The hydrochloric acid component in the smoke may contribute. Further details on exposure to zinc chloride are provided by Milliken, et al. (1963).

The effects of inhaltion of zinc chloride in smoke from smoke bombs have also been described by Schmal (1974) who reported on 11 cases, of which 2 had very severe reactions including edema of the lungs. However, no severe sequelae were seen. In one case, however, it was almost two years before the lung function was normalized.

Batchelor, et al. (1926) made an extensive investigation of workers exposed to zinc in a smelter in New Jersey. The authors pointed out that this smelter was well suited for studies on chronic effects of zinc since the amounts of lead, cadmium, and arsenic in the ore were very low compared with other types of zinc ores processed in other parts of the U.S. Of a total work force of 1,620 men, a number of workers were selected from different work areas for the special studies. Twelve men were selected from bag rooms where zinc oxide was handled. From a zinc oxide packing house five men were selected; four of them never wore respirators. From another zinc oxide plant two men were selected and two men were selected from a plant handling metallic zinc. Finally, three workers from a lithopone packing house were selected. A number of determinations of zinc concentrations in air were made. In the bag house an average concentration of 14 mg/m^3 was observed. In other workplaces mean concentrations were generally below 35 mg/m^3. In the zinc dust plant a maximum concentration of 130 mg/m^3 was measured. The 24 subjects underwent a number of examinations which included x-rays, physical examinations, interviews, blood pressure measurements, and measurements of zinc in blood, urine, and feces. Regarding the laboratory findings, it may be noted that 14 of the 24 men showed a slight leukocytosis; hemoglobin was reported to range between 72 and 97 percent with an average of 81 percent (100 percent is assumed to be 160 µg/l). Twenty-four-hour zinc elimination via feces in controls was reported to vary from about 4 to 20 mg, with an average of 9.32 mg, which is in good agreement with present daily values. In the exposed subjects, 24-hour excretion of zinc via feces averaged 46.8 mg which indicates an exposure via the gastrointestinal tract or massive excretion into the intestine. The conclusion of the authors was that the workmen could be exposed to zinc compounds in a smelter for decades without any symptoms or chronic disease.

Chmielewski, et al. (1974a,b) reported on the examination of 60 shipyard workers who were exposed to zinc oxide in different operations. As a control group, 10 healthy subjects who did not work in the shipyard and 10 shipyard workers not exposed to zinc oxide were used. Interviews showed that most of the workmen had experienced metal fume fever several times. Exposure levels varied between 1.7 and 18 mg/m^3 of zinc oxide, but a maximum value of 58 mg/m^3 was found during welding on one occasion. Laboratory investigations showed a tendency to leukocytosis, but other laboratory investigations gave no conclusive results. Some enzyme activities were determined before work and after work. Also in control groups changes were noted during the workday. It is obvious that in this study many of the workers must have been exposed to substances other than zinc oxide. For example, levels of nitrogen oxides were high in some workshops, the highest being 120 mg/m^3, with mean concentrations varying from 2 to 20 mg/m^3. Also, the total dust was high in some workplaces with levels around 100 mg/m^3 in several places.

Pistorius (1976) studied the effect of zinc oxide on rat lungs in an 84-day study. The rats were divided into groups so that they were exposed for 1, 4, or 8 hours a day to a concentration of 15 mg/m^3 of zinc oxide, at particle size less than 1 micron. A number of lung function tests were performed after 2, 4, and 7 weeks and at the end of the experiment. For most parameters there was no difference between controls and exposed animals, but in specific conductance and difference volume there was a significant decrease after two weeks. Further exposure resulted in all three exposure groups getting closer to the control values. Paradoxically the animals with the 1-hour exposure per day had the lowest values and the 8-hour exposure animals the highest values. The results were attributed to bronchial constriction. The author also explained the improvement in lung function with extension of exposure as a result of an increased elimination from the lung due to an increase in macrophages.

Pistorius, et al. (1976) exposed male and female rats for 1, 14, 28, and 56 days to zinc oxide dust at a concentration of 15 mg/m^3, 4 hours/day, 5 days/wk. Animals were killed 24 hours after the last exposure and the zinc content of the lungs, liver, kidneys, tibia, and femur was measured. After a single exposure the total zinc content of the lung in males and females was about 46 and 49 µg, respectively. In the male rats similar amounts were found after the longest exposure, whereas in female rats the zinc content after repeated exposure was lower in all groups than after the first exposure. Zinc concentrations were highest in the lung after 1 and 14 days of exposure. In liver and kidney there were no major changes during the experiment, but it should be pointed out that a nonexposed control group was not followed. No differences could be noted in bone. Histological examination of the lungs showed infiltration of leukocytes and inflammatory changes; after 28 and 56 days of exposure, an increase in macrophages could be shown. These studies indicate that there is a rapid elimination of inhaled zinc from the lungs, and that the absorbed zinc is rapidly eliminated from the body through the homeostatic mechanism.

Zinc stearate is a compound other than zinc oxide which is often encountered in the plastic industry and is suspected of causing lung disease. Votila and Noro (1957) reported on a fatal case involving a worker employed for 29 years in a rubber plant. The autopsy showed the cause of death was a diffuse fibrosis of the lungs with histochemical examination of the lungs showing increased deposits of zinc. However, no quantitative determinations of the zinc content of the lung were made. The role of zinc stearate as a cause of chronic lung disease has since then been discussed by Harding (1958) and by Weber, et al. (1976). Harding gave rats intratracheal instillations of 50 mg of zinc stearate which caused the deaths of about half of the animals. In the survivors (living up to 259 days after instillation of the compound) fibrosis could not be detected. Harding also found that the zinc stearate had disappeared from the lungs within 14 days. Weber, et al. described autopsy findings in a man who was employed for the last eight years of his life in a plastics industry and who was exposed to zinc stearate. Fibrosis was found in the lungs with the zinc content of 62 mg/kg of lungs on a dry weight basis (Weber, et al. 1976). The same authors found that 30 persons from the same area had concentrations between 3.3 to 69.3 mg/kg of zinc in lungs. The man had also had other occupations, but his exposure to silica quartz in another occupation could not explain the fibrosis. The authors concluded that zinc stearate could not have caused the fibrosis, one reason being that the zinc content of lungs was within the normal limits. However, as pointed out by Harding (1958), zinc stearate is cleared relatively rapidly from the lungs, so a normal content of zinc in the lungs does not exclude the possibility that zinc stearate might have contributed to this disease.

Tarasenko, et al. (1976) exposed rats to a single intratracheal administration of zinc stearate in a dose of 50 mg, and found, like Harding, that 50 percent of the animals died after that dose. In animals that survived, pathological changes were seen in the lungs two months later. Still later a picture of chronic alveolar emphysema and bronchitis was seen. According to the report, doses of 10 mg and 5 mg were also given but the results were not presented.

The hazards of keeping food or liquids in galvanized containers were illustrated in a report by Brown, et al. (1964) on two outbreaks of food poisoning, assumed to be caused by zinc in California in 1961. In one instance the food poisoning was caused by keeping chicken with tomato sauce and spinach in galvanized tubs. In the other instance a punch drink had been kept in galvanized containers. Zinc content of the food was estimated by repeating the preparation of the meal. After 24 hours of storage the mixture of chicken and tomato sauce contained close to 1,000 ppm of zinc. The other poisoning was caused by punch containing 2,200 mg/l of zinc. It was calculated that the doses of zinc would be 325 to 650 mg. In the first instance symptoms occurred 3 to 10 hours after ingestion. Severe diarrhea with abdominal cramping was the main symptom. Vomiting was not common, whereas after drinking the punch the first symptoms were nausea and vomiting which occurred within 20 minutes after ingestion. Diarrhea was also noted in the latter instance. No after effects were observed. It may be noted that in the first instance zinc was ingested with food and the delay in symptoms may have been caused by a simultaneous occurrence of vegetables and meat, whereas in the second instance a more acute effect occurred since only drinks were served. Cadmium was not determined in either of these studies. Galvanized materials often contain relatively large amounts of cadmium.

Murphy (1970) reported on a 16-year-old boy who tried to promote wound healing by ingesting a large amount of zinc, 12 g of elemental zinc mixed with peanut butter. The zinc was ingested over a 2-day period in doses of 4 and 8 g per day. He became lethargic, had difficulties in staying awake, experienced a slight staggering of gait, and noted problems in writing legibly. Nine days after the ingestion of the first dose of zinc, he was admitted to a hospital. Neurological and laboratory examinations did not reveal anything abnormal, except a slight rise in serum-amylase and lipase. Zinc in whole blood was slightly elevated whereas serum zinc was within the normal range. There was no increase in the zinc level of cerebrospinal fluid. He was treated with dimercaprol and there was a rapid decrease of whole blood levels of zinc to subnormal values. This treatment removed his lethargy. The author's conclusion was that this case showed symptoms indicating an influence of zinc on the pancreas and the cerebellum, but that these effects were easily reversible and no sequelae were seen.

Chunn (1973) studied a group of hospitalized children with anemia. There were three children who had levels of zinc in urine above 1 mg/l, but it was not stated by which method the zinc concentrations were determined. The author attributed the common factor for anemia and high zinc excretion in these children to the fact that all three children played with metal cars made from an alloy containing zinc. In a test it was found that placing a toy car in warm water resulted in zinc levels of 1.8 mg/l in water. The author suggested that the zinc could have been ingested by the children imbibing water when they were in the bath tub playing with toys.

Pories, et al. (1967) gave 10 young men with wounds after removal of pilonidal sinuses, daily doses of 150 mg of zinc as the sulfate for 43 to 61 days. Compared to 10 men not being supplemented by zinc, wound healing was accelerated among the men given zinc. Except for some gastric discomfort, no ill effects were noted. However, the authors did not present any results of laboratory examinations. In the same report, it is mentioned that in other studies zinc sulfate was given orally in the same dose for more than 22 months.

Greaves and Skillen (1970) reported on 18 patients who were given daily doses of zinc sulfate corresponding to 150 mg zinc per day for between 16 and 26 weeks as treatment for venous leg ulcerations. Before treatment the plasma zinc levels varied between 0.68 and 1.2 mg/l, and after completion of treatment the levels were between 0.84 and 1.92 mg/l. During the study a number of laboratory investigations were undertaken on several occasions, but copper levels were not determined. No ill effects could be noted from the treatment with zinc and there were no changes in hemoglobin or serum enzymes.

In animal experiments it has been shown that zinc may interfere with copper metabolism and that when the intake of copper is low, excessive zinc may induce a copper deficiency and anemia (NRC Chapter 9 pp. 256-257; Underwood, 1977; Hamilton, et al. 1979; Murthy and Petering, 1976). The animal data indicate that prolonged excessive intakes of zinc may constitute a hazard in patients treated with oral zinc supplements.

Hallbook and Lanner (1972) gave 13 patients with leg ulcers zinc sulfate in oral daily doses of 600 mg, corresponding to 135 mg of zinc per day. Treatment lasted for 18 weeks. Fourteen patients were given a placebo. Blood counts, liver function tests, and urine analysis did not show any significant differences between patients given zinc and the placebo. Serum levels of zinc rose among patients with an initial level of <1.1 mg/l from an average of 0.95 mg/l to 1.57 mg/l after six weeks of treatment, but no further increase was noted. Among patients with an initial serum level >1.1 mg/l no increase in zinc levels was noted during the 18 weeks of treatment. Copper concentrations were not measured.

During the last years there have been some reports on copper deficiency in human beings after treatment with zinc. Prasad, et al. (1978a) and Porter, et al. (1977) have reported hypocupremia after a long-term treatment with zinc sulfate in doses of 660 mg/day, i.e., 150 mg zinc per day. In both cases it was easy to correct the hypocupremia. No chronic effects of the treatment were seen, but Porter, et al. pointed out that the daily doses of 660 mg zinc sulfate may be too high for long treatment. It should be noted that in both studies patients with severe diseases were treated (sickle-cell anemia and coeliac disease).

Zinc poisoning has occurred in cattle. In the outbreak described by Allen (1968), the zinc poisoning of cattle was caused by dairy nuts which had been contaminated by error with zinc so that the zinc concentration was 20 g/kg. It was stated that the cows had an intake of about 7 kg/day of these dairy nuts, which would correspond to an intake of 140 g of zinc per cow per day. Exposure was only for a couple of days but it resulted in severe enteritis. One one farm, 7 out of 40 cows were so severely affected that they died or had to be slaughtered. The post-mortem findings showed severe pulmonary emphysema with changes in both myocardium, kidneys, and liver. There were also some indications that copper levels were lower than normal. Zinc concentrations in liver were extremely high, measured on a dry matter basis, 1,430 and 2,040 mg/kg in two analyzed livers.

Lead poisoning has occurred in horses living near lead-zinc smelters. In foals, some symptoms, lameness and joint afflictions especially, have been described and related to exposure to zinc in areas near smelters. Willoughby, et al. (1972) gave foals a diet containing 5,400 mg/kg of zinc and another group received, in addition, lead in the amount of 800 mg/kg. The groups were compared with a control group and a group given only the excessive amount of lead. It should be mentioned that the groups consisted of only 2 or 3 animals each. In three animals given excessive amounts of zinc, bone changes, especially in the epiphyseal areas of the long bones, were noted as a first sign. Later the animals had difficulties in standing and walking. In animals given lead and zinc the symptoms associated with exposure to zinc dominated. There were fewer effects from the exposure to lead and zinc than in animals given only lead. It should be noted that in this experiment, exposure to zinc was extremely high, but taken together with the other reports on actual findings in animals living near smelters, it is obvious that exposure to zinc in high amounts may constitute a hazard to horses.

Aughey, et al. (1977) gave zinc (as the sulfate) to mice for up to 14 months in drinking water at a concentration of 500 mg/l. The concentrations of zinc in feed for controls and exposed animals were not stated. That zinc is readily absorbed was seen by a rapid rise in plasma concentrations of zinc during the first days of exposure. During six months no difference between controls and exposed animals could be shown regarding zinc concentrations in the liver, spleen, and skin nor was there any difference between the sexes. Histological examination showed that several endocrine glands were affected by the administration of zinc. Hypertrophy was found in the adrenal cortex; in the pancreatic islets and in the pituitary gland changes consistent with hyperactivity were noted.

Kang, et al. (1977) gave rats, by pair-feeding, diets containing 1.3, 55, and 550 mg zinc/kg of feed for four weeks. The animals were killed after that time and tissue concentrations of zinc and a number of other metals were determined. The low zinc diet gave typical signs of zinc deficiency, whereas there was no difference in weight gains and food efficiency ratios in the two groups given higher amounts of zinc; this fact, according to the authors, suggested that the highest level (550 mg/kg) was not toxic. Liver and kidney concentrations of zinc were slightly higher in the group given the largest amount of zinc, but no difference was noted in the heart. Iron concentrations in liver were inversely related to the intake of zinc, whereas no difference in copper concentrations or magnesium concentrations in the liver could be seen between the two highest zinc levels. In the kidney there was also a tendency for decreasing iron concentrations with increasing zinc intakes as well as for copper, but there was practically no difference between the two highest dose levels, nor was there a difference in magnesium.

In pigs given zinc in the diet in concentrations ranging from 500 to 8,000 mg/kg, Brink, et al. (1959) found that signs of toxicity in the form of weight gain and feed intake were seen at levels above 1,000 ppm. In pigs, given from 2,000 ppm and higher, deaths occurred as soon as two weeks after exposure and severe gastrointestinal changes were seen with hemorrhages. There were also signs of brain damage due to hemorrhages. Changes in the joints were also seen, mainly in the form of swollen joints. In liver samples from these pigs, levels of zinc above 1,000 mg/kg wet weight were found.

In a woman given total parenteral nutrition after an operation, acute zinc poisoning occurred due to an error in prescription. During a period of 60 hours she received 7.4 g of zinc sulfate. She became acutely ill with pulmonary edema, jaundice, and oliguria, among other symptoms. The serum zinc concentration was 42 mg/l. In spite of treatment she remained oliguric and hemodialysis did not improve renal function. She died after 47 days of illness (Brocks, et al. 1977).

It has been reported that zinc and copper could be introduced in excessive amounts into the blood during hemodialysis (Blomfield, et al. 1969). Petrie and Row (1977) described nine cases of anemia in dialysis patients due to the release of zinc from a galvanized iron tubing in the dialysis system. Copper levels were not measured in these cases but there was a rise in hemoglobin concentrations after removal of the source of zinc.

Acute effects of hemodialysis have been described by Gallery, et al. (1972). A woman on home dialysis used water stored in a galvanized tank and two hours after the first dialysis at home she had symptoms including nausea, vomiting and fever. Similar severe symptoms were experienced by her at two subsequent dialyses, but subsided between dialyses. Dialyses at the hospital were then done without any symptoms, but she had symptoms again when she started dialysis at home. At new admission to the hospital she was found to be severely anemic. It was then found that the zinc concentration in the tank water was 6.25 mg/l. The patients's zinc concentration in red cells was 35 mg/l and after six weeks dialysis in the hospital it was reduced to 12 mg/l. During the same period plasma levels decreased from 7 mg to 1.58 mg/l. Blood copper was not decreased.

Teratogenicity, Mutagenicity, and Carcinogenicity

The relationship between zinc and cancer has been reviewed earlier by the NRC (1978) (Chapter 7 pp. 208-209, Chapter 9 pp. 231-234 and Chapter 10 pp. 258-261) and by Sunderman (1971). It was concluded that during certain experimental conditions, injections of zinc salt into the testes could induce testicular tumors. There was no evidence that zinc given via the oral route or parenterally could cause tumors. However, zinc is of interest with regard to cancer since zinc seems to be indirectly involved by being of importance for the growth of tumors. As discussed earlier zinc is necessary for DNA and RNA synthesis. It has been shown that in zinc-deficient rats tumor growth was reduced (Petering, et al. 1967; DeWys, et al. 1970). These earlier findings have recently been confirmed in other studies.

The effect of different levels of dietary zinc on the development of chemically-induced oral cancer in rats has recently been studied by Wallenius, et al. (1979) and Mathur, et al. (1979). In the study by Wallenius, et al. (1979), three groups of female rats were fed diets for three weeks which contained 15 mg/kg, 50 mg/kg, and 200 mg/kg of zinc, respectively. The palatal mucosa was then painted with the carcinogen 4-nitro-quinoline-n-oxide three times a week. The animals were killed after cancer could be observed macroscopically in the oral cavity. It was found that in animals given the diet with the highest level of zinc, the macroscopical signs of cancer appeared earlier, as compared with animals given lower amounts of zinc. In the study by Mathur, et al. (1979), a similar design was used but the levels of zinc in that experiment were 5.9, 50, and 260 mg zinc/kg diet. The groups of animals were sacrificed and blood, liver, and palatal mucosa were sampled 3, 9, 13, and 23 weeks after the beginning of exposure. Control animals were killed at the same time. The carcinogen had been applied three times a week. It was found that after three weeks the animals with the lowest zinc intake, which was regarded as producing zinc deficiency, showed more advanced histological changes than animals given 50 or 260 mg/kg diet of zinc. After 20 weeks' application of the carcinogen, there was no difference in the development of tumor between zinc deficient and zinc supplemented groups. It may be noted that both in the low and high level zinc groups, carcinoma _in situ_ and fully developed carcinomas were found. Whereas, in the group given 50 mg zinc/kg diet, regarded as an adequate level, even after 20 weeks only moderate dysplasia was seen. The groups studied were quite small and thus did not allow any detailed statistical analysis. The results were interpreted to mean that zinc deficiency made the animals more susceptible to the induction of cancer but at the same time caused a slower growth rate of tumors, and that a high zinc intake initially gave some protection against the development of tumors but that later excessive zinc intake promoted tumor growth.

Another example of the importance of zinc deficiency for the development of cancer is the study by Fong, et al. (1978). One group of rats was fed a diet containing 60 mg/kg of zinc and one group of rats was fed a diet containing 7 mg/kg of zinc. After 12 weeks on these diets the carcinogen methylbenzylnitrosamine was administered by intragastric intubations twice weekly in doses of 2 mg/kg body weight for 12 weeks. In another experiment the design was similar but the carcinogen was administered after four weeks with the length of exposure of nine weeks. Some animals were killed at the end of exposure and some animals were killed five weeks later. In a third experiment the carcinogen was given for four weeks and animals were sacrificed 63 days after the start of exposure. Finally, there was one experiment where the exposure was only for two weeks for a total of four doses of the carcinogen. As expected, zinc levels in the esophagus were lower in zinc deficient animals than in controls, but they were also lower in animals on an adequate intake of zinc, but which were given the carcinogen. A general finding was also that in zinc-deficient animals more carcinomas of the esophagus were found than in animals fed an adequate intake of zinc. It was also noted that in the groups given the lowest doses of the carcinogen, the difference between groups was most significant; a total of eight doses gave figures of 79 and 29 percent, respectively, for tumor incidence and at a total of four doses the corresponding figures were 21 percent and zero (0) percent.

Regarding human beings, there in no evidence that zinc deficiency in itself has any etiological role in human cancer. However, many studies have been performed on the levels of zinc in both malignant and nonmalignant tissues in human beings. The zinc concentrations have been found to be both low and high and no definite pattern has occurred (NRC [1978] Chapter 9 pp. 231-234 and Chapter 10 pp. 259-261). As an example it has been shown that in cancer of the esophagus in human beings zinc concentrations were lower than normal which is in accordance with the above mentioned experiments on rats (Lin, et al. 1977). However, there is one organ in the human being where there seems to be a more consistent pattern, the prostate gland. It has been discussed earlier that zinc concentrations in the prostate normally are very high. There has been a consistent finding that in cancer of the prostate there is a decrease in zinc in the carcinomatus tissue of the prostate.

In the study by Habib, et al. (1976), zinc concentrations in the neoplastic tissue were less than half of the concentrations in normal tissue or in hypertrophic prostates. These authors also reported that the cadmium levels were higher in the carcinomatous tissues than in the normal or hypertrophic tissue. High industrial exposure to cadmium has been implicated as a possible cause of prostatic cancer and since there are interactions between cadmium and zinc, this might have some bearing on the problem of the relationship between zinc and cancer of the prostate. Habib (1978) has reviewed the role of zinc in the normal and pathological prostate.

Regarding hyperplastic prostatic tissue, it may be noted that most reports have stated that there are the same concentrations of zinc in the hyperplastic tissues as in normal tissue. There is one exception; the study by Gyorkey, et al. (1967) found considerable increases in zinc levels in hyperplastic tissue - more than three times the normal.

The mutagenic effects of zinc have been discussed by the National Research Council (Chapter 10 p. 261) which could not find literature that suggested that zinc is mutagenic in animals and human beings nor have any new data appeared on this subject. The same conclusions are made with regard to teratogenesis. The greatest risk is related to zinc deficiency which might cause malformations. However, it is reasonable to assume that indirectly zinc might have an effect since long-term supplements with large amounts of zinc will cause disturbances in copper metabolism.

In a study by Cox, et al. (1969), it was shown that if rats were fed a diet containing 4,000 ppm of zinc during gestation, copper levels were reduced in the fetal body and liver whereas zinc concentrations increased. Ketcheson, et al. (1969) fed rats diets containing up to 5,000 mg of zinc/kg during gestation. Even at that level malformations were not observed, but there was a reduction in the copper concentrations of the fetal liver.

A brief statement in a report by Kumar (1976) states that in a small group of women supplements of zinc administered during the third trimester of pregnancy in a dose of 100 mg of zinc sulfate per day (23 mg zinc per day) caused premature births and one still-birth in four consecutive subjects. Kumar then made studies in rats and gave them a daily supplement of 100 ppm zinc orally (it is not quite clear how the dose was calculated, but it is stated in the report "received additionally 150 ppm zinc as a 2 percent zinc sulfate solution"). The concentration of copper and other nutrients in the diet was not stated. In the zinc-supplemented animals there was a significant increase in the number of resorptions of the implantations. Supplementation for pregnant women has been recommended, but due to the known interaction between zinc and copper, excessive zinc intakes during prolonged times could have an adverse effect on the fetus. It is well documented in animal experiments that zinc deficiency during pregnancy might have an adverse effect on the fetus (NRC Chapter 7 pp. 179-180).

INTERACTIONS OF ZINC WITH OTHER METALS

As has already been discussed in the section concerning effects of excessive intakes of zinc, interactions between zinc and other metals may occur. It was demonstrated that excessive intakes of zinc could influence the metabolism of iron and copper, but it is also possible that excessive intakes of other metals may also have an influence on the metabolism of zinc. Such metal-metal interactions have recently been discussed at an international meeting and reported (Nordberg, 1978). Interactions between zinc and other metals have also been reviewed by Underwood (1977) and NRC (Chapter 7 pp. 186-187).

Cadmium

Interactions between cadmium and zinc were extensively discussed in the NRC report (Chapter 10 pp. 261-268) and the literature up to 1974 was reviewed and discussed. It was concluded that exposure to cadmium would cause changes in the distribution of zinc with increases in liver and kidney where cadmium also accumulates. In animals on marginal zinc intakes there could be a zinc deficiency in certain organs parallel with the increase in liver and kidney. It has also been shown that in both human beings and horses the increase in renal concentrations of zinc is parallel to the increases in cadmium and that this increase is nearly equimolar up to cadmium concentrations of about 60 mg/kg wet weight. These earlier findings have recently been confirmed in new studies both in human beings and in horses (Elinder and Piscator, 1977, 1978). The increase in renal zinc is also related to the occurrence of cadmium in metallothionein. It has recently been shown that whereas at low levels of cadmium in the kidney there are about equimolar amounts of zinc and cadmium in metallothionein, with increasing cadmium concentrations the ratio of cadmium to zinc will increase. It was also shown that at a level of about 200 mg/kg wet weight of cadmium the amount of zinc in metallothionein would be close to zero (Nordberg, et al. 1979) and that corresponds to the critical level which has been estimated for renal cadmium related to the occurrence of renal tubular dysfunction (Friberg, et al. 1974).

Although a large number of animal studies have been performed, there might be some difficulties in drawing conclusions with regard to the human situation. A review of the literature by Elinder and Piscator (1978) showed that there are clear differences between some large mammals (e.g., man, horse) compared to small laboratory animals. In the rat especially (the most commonly used laboratory animal), exposure to cadmium will result mainly in an increase in hepatic zinc, whereas the increase in renal zinc is rather small. On the other hand, exposure to cadmium causes increases in renal copper concentrations. Such differences make it reasonable to conclude that one must be cautious when drawing conclusions from experiments done with rats. The differences between species are illustrated in Figure 1. Zinc deficiency alone is known to cause effects on the fetus. If animals are exposed to cadmium during the gestation period, this may also influence the mineral distribution in the fetus. Pond and Walker (1975) showed that both low zinc and copper concentrations and decreases in birth weight were found in rat pups that had been given cadmium orally. Since cadmium does not pass the placental barrier to any significant extent, this is thought to be due to retention of zinc in the dam parallelling the accumulation of cadmium as previously mentioned. Data by Choudhury, et al. (1978) indicate that in the rat fetus a decrease of copper and iron occurs before the zinc levels are affected.

Lal (1976) found that oral exposure to cadmium could cause testicular and pulmonary lesions in rats on a marginal intake of zinc, 5 mg/kg feed, whereas such lesions were not seen when the diet contained 40 mg zinc/kg. The exposure in that experiment was 17.2 mg/l of cadmium in drinking water. Zinc concentrations in the testes of zinc-deficient animals were 104 mg/kg, compared to 143 mg/kg in the animals at the higher level of exposure.

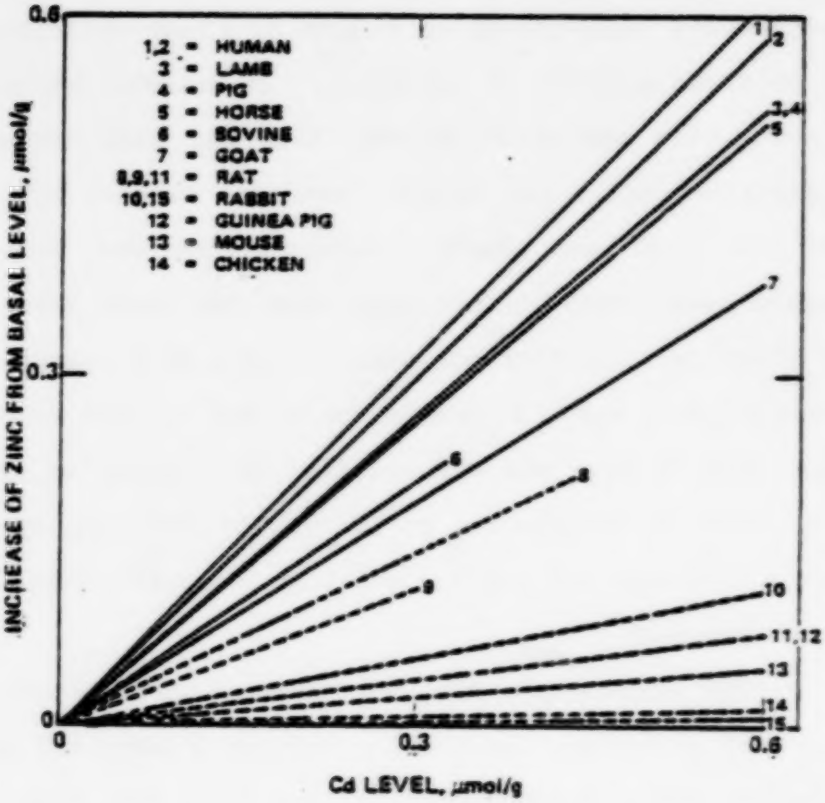

FIGURE 1

Increase of zinc as a function of increasing cadmium concentration in kidney of 11 different species. The data are taken from nine publications. The references are in the paper by Elinder and Piscator (1978).

Copper

It has been mentioned earlier that excessive intakes of zinc may cause copper deficiencies in human beings and result in anemia, which can be easily corrected by decreasing the intake of zinc and giving copper supplementation. It has also been suggested by Klevay (1975) and Klevay and Forbush (1976) that the ratio between copper and zinc in the American diet contributes to coronary heart disease. The main reason for this may be that the copper content of the typical American diet is less than the requirement. These theories have not been substantiated, even though Klevay (1973) found that in rats hypercholesterolemia occurred with an increasing zinc-copper ratio in the diet. It has since been shown that it is the copper status that is the main factor with regard to cholesterol levels (Petering, et al. 1977; Murthy and Petering, 1976; Allen and Klevay, 1978).

Evans, et al. (1974) found that in zinc deficient rats excessive amounts of copper did not influence the uptake of ^{65}Zn from the gut, but in zinc-supplemented rats excess copper had an influence on the uptake of ^{65}Zn. The authors tried to explain the findings by suggesting that in the zinc deficient rats a larger number of zinc binding sites on plasma albumin would be available and that at such sites there would be no competition with copper.

Kinnamon and Bunce (1965) fed groups of rats a basic diet containing 18 mg/kg of copper, 70 mg/kg of zinc, and less than 1 mg/kg of molybdenum. To these diets zinc, copper, or molybdenum and combinations of these metals were added in amounts of 100 mg/kg of copper, 1,800 mg/kg of molybdenum, and 5,000 mg per kg of zinc. The length of the experiment was seven weeks. At the end of the experiment all animals were given an injection of radioactive zinc. After four days the animals were killed. It was found that an increase in dietary zinc resulted in an increased bone retention and decreased urinary excretion of the isotope but that even the very high level of copper or molybdenum did not influence the retention or tissue distribution of the isotope. These data indicate that the levels of zinc retained and excreted are affected only by zinc dietary levels and not by levels of copper or molybdenum ingested at the same time as zinc.

Calcium

The influence of calcium on absorption of zinc from the gut was discussed by NRC (1978) (Chapter 7 pp. 184-185). It was concluded that calcium levels in the diet do not influence zinc absorption except for some indications that calcium could have an influence when zinc intake is marginal. Also, Underwood (1977) has reviewed the relationships between zinc and calcium. The study by Hurley and Tao (1972) shows an interesting example of interaction between zinc and calcium. Beginning on the first day of gestation, female rats were given either a zinc-deficient diet containing 0.4 mg zinc per kg or a zinc-deficient and calcium-deficient diet which contained the same amount of zinc but 15 mg of calcium per kg of feed. The animals were killed on the 21st day of gestation, and the fetuses were removed and examined. The results showed that in females deficient in both calcium and zinc the resorption rate in the uterus was lower and there was a larger number of live births per litter than among the rats given only the zinc-deficient diet. Eighty-three percent of the fetuses from females on the zinc- deficient diet showed malformations whereas the corresponding figure for zinc-deficient and calcium-deficient group was 57 percent. Analysis of maternal bone showed there was a reduction in both ash weight and total calcium content of the femur in the females given the zinc-deficient and calcium-deficient diet. This was interpreted as calcium being withdrawn from the bone during pregnancy to provide calcium to the fetus. There was also lower zinc content in the bones of rats on the calcium-deficient diet. This suggested that zinc was released from bone during the release of calcium. This zinc could then be available and transported to the fetus, whereas in animals on a zinc-deficient and high calcium intake there would be no release of zinc from bone and thus the large amount of zinc stored in bone would not be available to the fetus. This study shows how two essential metals can interact with each other.

Iron

As mentioned earlier, high intake of zinc may affect iron metabolism, but much less is known about the effects of iron on zinc. Sherman, et al. (1977) gave pregnant rats diets containing 5, 29, and 307 mg/kg of iron. Eighteen days after parturition both the dams and pups were killed and examined. It was found that the zinc to copper ratio in spleen increased in dams but tended to decrease in the pups as a result of iron restriction. In the pups the zinc to copper ratio was considerably lower in the liver of iron-deficient animals but in the dams no differences were seen between groups with high and low iron intake. In the iron-deficient pups increased levels of serum lipids were associated with decreased ratio of zinc to copper in the tissues.

Hamilton, et al. (1978) studied the intestinal absorption of zinc in iron-deficient mice and found that zinc uptake from the gut was inhibited by adding iron to the duodenal loop system used. It was concluded that there were some common mucosal binding sites for both iron and zinc.

Lead

It was mentioned earlier that in horses there can be simultaneous exposure to lead and zinc and there seem to be some interactions; there was a lower uptake of lead in animals with high intake of zinc. Cerklewski and Forbes (1976) studied the influence of three dietary levels of zinc (8, 35, and 200 mg/kg) on rats given 50 and 200 mg lead per kg feed. They found that with higher dietary zinc concentrations the symptoms of lead toxicity decreased. The lead concentrations in tissues were lower in animals with high zinc intake, but also the hematological changes were less. It was concluded that the main interaction was in the gut.

Lead will also have an influence on the zinc concentrations in tissues as was shown by El-Gazzar, et al. (1977). Rats were given drinking water containing 5 and 50 mg/l of zinc and 100 mg/l of lead. Lead exposure decreased the plasma zinc in the low level zinc group but increased erythrocyte zinc. Further exposure caused reduced plasma zinc levels also in the high zinc level group. There were also reductions in the zinc levels in liver and tibia of both groups. There was no change in the brain concentration of zinc.

An effect which has attracted great interest the last years is the effect of zinc on the activity of ALA dehydratase, a zinc dependent enzyme, in blood. In a number of studies both *in vivo* and *in vitro* it has been shown that zinc is antagonistic to lead regarding the ALA dehydratase activity, and that zinc decreases the excretion of ALA seen in lead-intoxicated rats (Abdulla, et al. 1976; Border, et al. 1976; Finelli, et al. 1975; Thawley, et al. 1978; Thomasino, et al. 1977).

Thawley, et al. (1977) gave rats a basic diet containing 30 mg/kg of zinc and 7 mg/kg of lead and then groups were given additions of 5,000 mg/kg of lead or 6,300 mg/kg of zinc and combinations thereof. These diets were also combined with two levels of calcium in the diet, 0.9 and 0.1 percent, respectively. The findings indicate that the increase in ALA excretion caused by lead was reduced by the additional exposure to the high level of zinc. The exposure to zinc caused larger reductions in serum iron than lead exposure. The most severe anemia was seen in animals on a high lead and high zinc intake together.

Interactions Between Zinc and Drugs

In the previous chapters it has been mentioned several times that contraceptive pills have an influence on zinc metabolism. The influence of oral contraceptives on the excretion of zinc in women on a low intake of zinc, copper, and iron was studied by Hess, et al. (1977). Urinary zinc excretion decreased in women both on contraceptives and not on contraceptives. The greatest change was in the contraceptive group with a decrease of 83 percent; a 62 percent decrease was seen for those not on contraceptives.

The usual intake of zinc in these women before the study started was estimated to be about 10 mg/day. During the study the intake averaged only 0.17 mg/day. At the beginning of the study, before the zinc intake was lowered, the average excretion of zinc in urine was 0.36 and 0.4 mg, respectively, for the group on contraceptives and for the control group. These data indicate that whereas contraceptives will have relatively little influence on zinc metabolism during normal zinc intake, they may have a more profound influence when the zinc intake is low. In this study the zinc intake was extremely low.

Many other drugs, especially drugs with chelating properties, may influence zinc metabolism. Thiazides and penicillamine can increase the excretion of zinc. Substances in food, such as phytate, can influence the absorption. Also, alcohol will have an influence on zinc metabolism especially if a state of chronic alcoholism has been reached with cirrhotic changes in the liver. Such cases often have low serum levels of zinc and an increased excretion.

CRITERION FORMULATION

Existing Guidelines and Standards

The National Institute of Occupational Safety and Health (NIOSH, 1975) has recently reviewed the occupational hazards of exposure to zinc oxide and no changes were suggested regarding the existing standard for zinc oxide of 5 mg/m^3. The American Conference of Government Industrial Hygienists (ACGIH, 1976) has an adopted threshold limit value (TLV) for zinc oxide of 5 mg/m^3 and the Occupational Safety and Health Administration (OSHA) (29 FR 1910.1000) has a workplace standard for zinc oxide of 5 mg/m^3, 8-hour time-weighted average. The TLV value has also been adopted in other countries. For zinc chloride a limit of 1 mg/m^3 has been adopted by ACGIH and OSHA also adopted a standard of 1 mg/m^3 for zinc chloride.

The present standard for drinking water, 5 mg/l, is based on organoleptic effects, i.e., some people will recognize the bitter taste caused by zinc present at such levels. The World Health Organization (WHO) has also proposed that the level should be 5 mg/l; however, the USSR has established a limit for zinc at 1 mg/l for other than health reasons (NAS, 1977).

There is no acceptable daily intake for zinc in food. As mentioned earlier, zinc is an essential nutrient and there has been no reason to restrict the zinc levels in food.

In 1974, the National Academy of Sciences recommended that adults should have an intake of 15 mg of zinc per day, that pregnant women should have an intake of 20 mg/day, lactating women should have 25 mg/day, and that pre-adolescent children should have 10 mg/day of zinc (Table 3) (NAS, 1974).

Current Levels of Exposure

It has been well established in several studies that the present intake of zinc via food for the adult U.S. population is from 10 to 20 mg/day. For the majority of the population, the intake of zinc via drinking water will be only a few percent of the intake via food, but for some individuals the zinc concentration in tap water may cause an additional daily intake of 2 to 10 mg of zinc. The average exposure to zinc via ambient air will, even in the vicinity of zinc emitting industries, be in the order of only a few tenths of a milligram. Smoking will contribute even less.

Special Groups at Risk

Since zinc may interfere with copper and other minerals, excessive intakes of zinc by people with a tendency to copper deficiency might cause reversible health effects. Patients treated for months or years with large oral doses of zinc salts, about 10 times the intake via food, for curing of various diseases caused by zinc deficiency or to promote wound healing may constitute a group at special risk. Infants with copper deficiency or low intakes of copper may constitute another risk group. Occupational exposure to zinc oxide fumes may cause acute reversible reactions which may put persons subjected to such exposure at special risk.

Basis and Derivation of Criterion

Zinc is an essential element and is not a carcinogenic agent. Studies on experimental animals and on human beings given zinc for

TABLE 3

Recommended Allowances (RDA) for Zinc*

Age (Yrs.)	mg/day	Age (Yrs.)	mg/day
0.0 - 0.5	3.0	4 - 6	10.0
0.5	5.0	7 - 10	10.0
1 - 3	10.0	11 - Adults	15.0

*Source: NAS (1980)

therapeutic purposes, together with observations of occupationally exposed persons, indicate that large doses of zinc can be tolerated for long periods if the copper status is adequate.

The toxicological data base for evaluating water quality criteria for zinc is inadequate. While there is no evidence that zinc is carcinogenic, there is a lack of usable data on chronic effects. Most animal studies reported in the literature fail to include specific exposure data, while studies with humans are generally either case reports of accidental high exposure or based on data from special groups (e.g., patients receiving high-dose zinc therapy for certain ailments).

The most common reported effect of high-level exposure to zinc is copper deficiency, which is readily reversible. The effect occurs at exposure levels at least an order of magnitude above the RDA for zinc. The data on special groups at risk for zinc-related copper deficiency are too sparse to include in criteria evaluation at the present time.

The presence of zinc in drinking water contributes to the RDA for this essential metal. Zinc is naturally present in water at concentrations generally well below the current drinking water standard of 5 mg/l, based on organoleptic effects. There are no known instances of adverse effects occurring at current standard. Therefore, it is reasonable that the current level of 5 mg/l be maintained for water quality criterion. As additional data become available, the current criterion will be reconsidered.

Long-term oral administration of zinc sulphate in daily doses of 135 to 150 mg of zinc has been well tolerated by patients given the compound to promote wound healing. In patients with metabolic diseases such treatment might cause reductions in serum copper levels. Using a safety factor as high as 10, this means that an additional intake of 15 mg of zinc does not constitute any health hazard. This corresponds to an intake of 2 liters of water containing 7.5 mg Zn/l. This concentration is above the present standard for drinking water which is 5 mg/l based on organoleptic effects.

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